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CONTENTS

Page

Aspects of the Action of Insulin. CHARLES H. BEST 433

Clinical Evaluation of Isoniazid. SEYMOUR S. CUTLER, BENJAMIN BURBANK and BIAGIO BATTAGLIA 444

Results Following Pulmonary Resection of Tuberculous Disease with Special Reference to Localized Necrotic Lesions. JAMES H. FORSEE, CARL W. TEMPEL and EDWIN L. SCOTT 463

Late Results of Treatment of the Solitary Dense Tuberculous Pulmonary Focus (Tuberculoma) without Resection or Chemotherapy. ROGER S. MITCHELL 471

Cholangiography. PHILIP G. KEIL, GEORGE J. HEGSTROM and SAMUEL J. ZOECKLER 479

The Management of Biliary Tract Disorders in Patients with Heart Disease. J. RUSSELL TWISS, R. FRANKLIN CARTER and SEYMOUR GOLDENBERG 484

Rheumatism and Arthritis: Review of American and English Literature of Recent Years (Tenth Rheumatism Review). Part I. WILLIAM D. ROBINSON, EDWARD W. BOLAND, JOSEPH J. BUNIM, DARRELL C. CRAIN, EPHRAIM P. ENGLEMAN, WALLACE GRAHAM, L. MAXWELL LOCKIE, MAX M. MONTGOMERY, CHARLES RAGAN, MARIAN W. ROPES, EDWARD F. ROSENBERG and CHARLEY J. SMYTH 498

Case Reports:

Hemolytic Anemia Secondary to Mesantoin. ISIDORE SNAPPER, DOROTHY MARKS, LAWRENCE SCHWARTZ and LESTER HOLLANDER 619

Black Widow Spider (*Latrodectus Mactans*) Poisoning Treated with d-Tubocurarine Chloride. GEORGE W. ALLEN 624

Neuropathic (Charcot) Joints Occurring in Diabetes Mellitus. W. M. SHEPPE 625

Xanthoma Diabeticorum. ESAR GORDON MARGOLIN 629

Effectiveness of N-Allylnormorphine in the Management of Acute Morphine Poisoning. FRANCIS J. MARX and JULIAN LOVE 635

Acute Hypertrophic Osteo-Arthropathy Associated with Subacute Bacterial Endocarditis. MALCOLM C. MCCORD and JOHN MONERLY 640

Editorial—The Changing Pattern of Syphilis 1941–1953 644

Reviews 650

College News Notes 656

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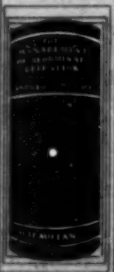

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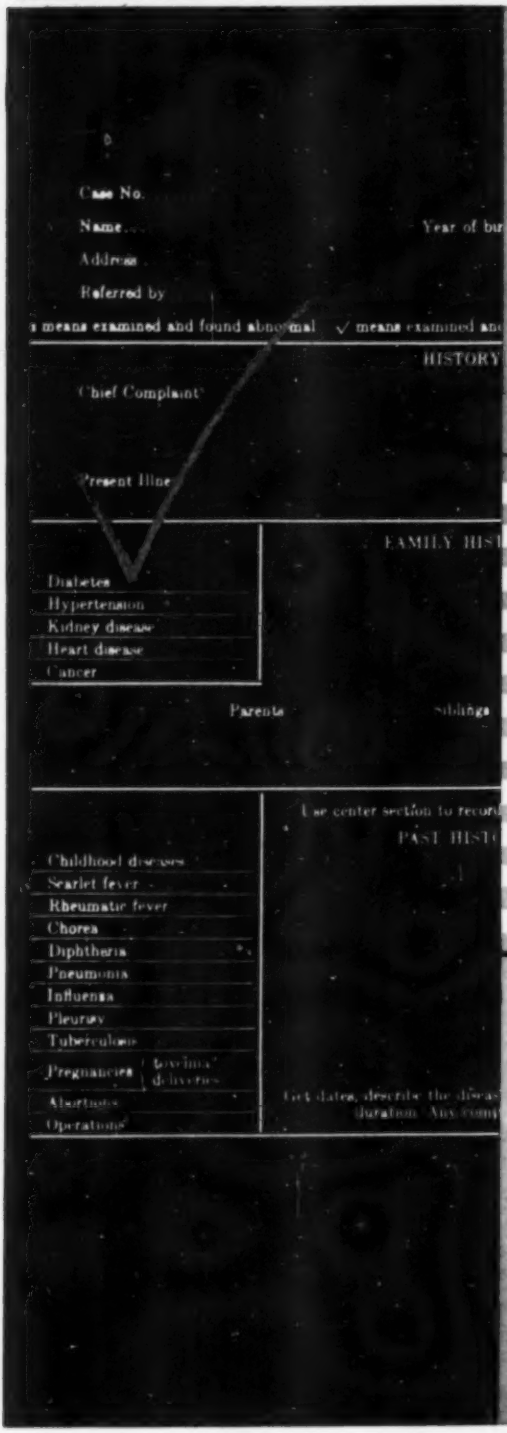

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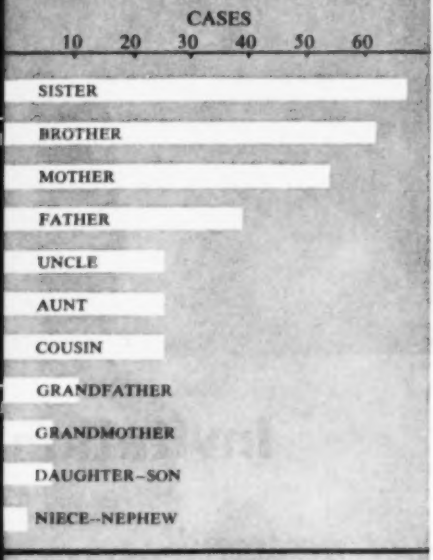

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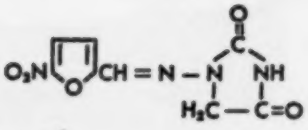

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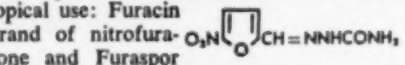

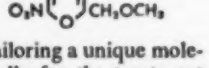

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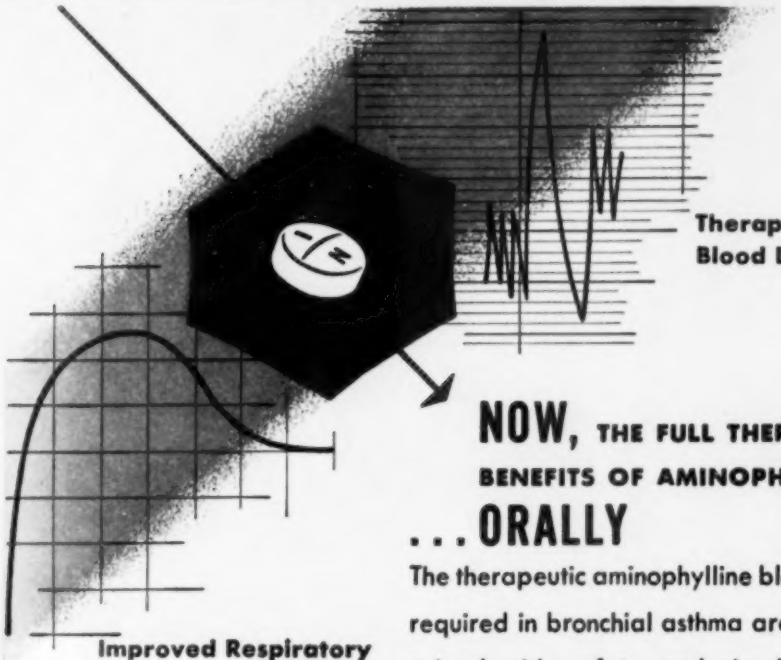


NOW, THE FULL THERAPEUTIC BENEFITS OF AMINOPHYLLINE ...ORALLY

The therapeutic aminophylline blood levels required in bronchial asthma are now obtained with safety and simplicity with Cardalin tablets providing 5 grains of *protected-aminophylline* per tablet—the highest concentration supplied for oral administration. Two protective factors minimize gastric irritation.

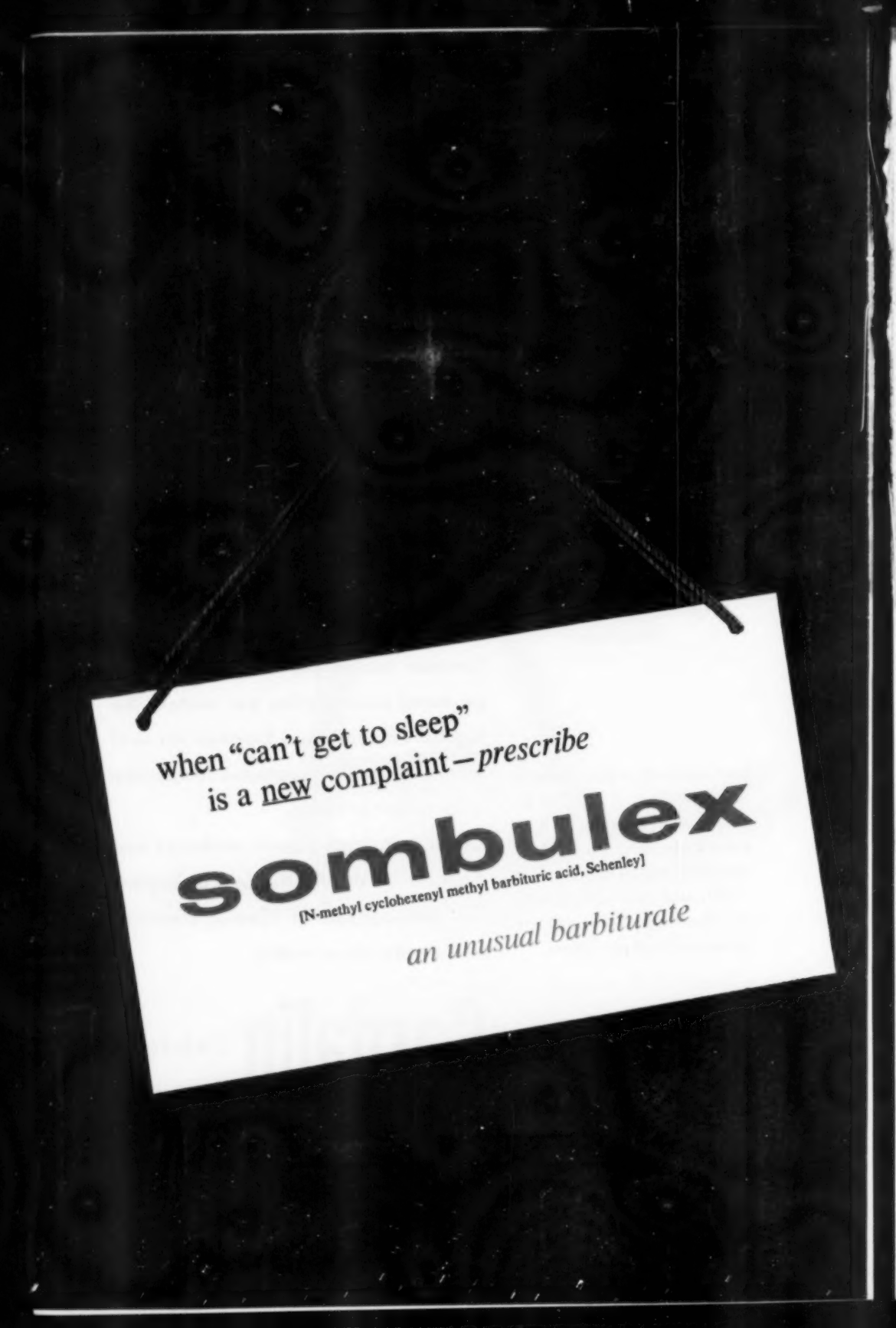
Cardalin tablets permit institution and maintenance of effective oral aminophylline therapy also in cardiac conditions and in edematous states.

Each Cardalin tablet contains:
Aminophylline . . . . . 5.0 gr.
Aluminum Hydroxide. . 2.5 gr.
Ethyl Aminobenzoate 0.5 gr.
Supplied: Bottles of 100, 500, 1000. Also available, Cardalin-Phen containing ¼ gr. phenobarbital per tablet.

Cardalin tablets

PATENT PENDING

IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS
Research to Serve Your Practice


when "can't get to sleep"
is a new complaint—prescribe
sombulex
[N-methyl cyclohexenyl methyl barbituric acid, Schenley]
an unusual barbiturate

sombulex* *is an unusual barbiturate*

because it works within 15 to 30 minutes and leaves the bloodstream within 3 to 4 hours, thus avoiding the danger of hangover for patients who do not need heavy barbiturate action.

When the stresses and strains begin to tell

...when the mind won't let the body rest, and patients complain for the first time..."Doctor, I can't get to sleep"... SOMBULEX is the prescription of choice for these first-time barbiturate patients. For them, 1 or 2 tablets taken with water or a warm beverage usually suffice to induce a night's refreshing sleep without hangover. Patients will not readily identify SOMBULEX as a barbiturate.

The unusual uses of **sombulex**

Because of its rapid yet nonpersistent action, 1 SOMBULEX Tablet will help restore *interrupted* sleep without subsequent hangover, or permit a relaxing cat nap before a busy evening. One SOMBULEX Tablet also will help the new night-shift worker adjust to a daytime sleeping schedule. NOTE: The action of SOMBULEX may be too short lived for the patient already dependent upon long-acting barbiturates. SOMBULEX is supplied in bottles of 100 tablets, each containing 0.26 Gm. (4 gr.) N-methyl cyclohexenyl methyl barbituric acid, *Schenley*.

SCHENLEY LABORATORIES, INC.

schenley

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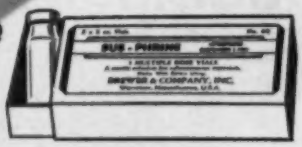
INTRODUCING...

a new 2 cc. vial package



In addition to the 5 cc. size individually packed

5 vials to package

For the prolonged relief of BRONCHIAL ASTHMA

SUS-PHRINE

AQUEOUS EPINEPHRINE SUSPENSION 1-200

Brewer

For the First Time

Epinephrine is available in an aqueous SUSPENSION To be injected SUBCUTANEOUSLY.

For the patient's

COMFORT

RELIEF

ECONOMY

Sus-Phrine, an aqueous suspension of epinephrine, is injected subcutaneously in doses of 0.1 to 0.3 cc. The slower absorption and longer action of the suspension requires fewer injections.

Sus-Phrine begins to be absorbed as soon as it is injected, and because it is a suspension, absorption takes place over a prolonged period and therefore it has a distinct advantage over aqueous solutions for subcutaneous injection.

Sus-Phrine is a specially processed stable suspension of epinephrine to make possible its packaging in 2 cc. multiple-dose vials (five to a package) and in 5 cc. vials (individually packaged) at a saving in cost to both physician and patient.

References:

1. Naterman, Hyman L. N.E.J. Med. 227: p. 736.
2. Unger, A. H., and Unger, L. G.P. 4:79 Dec. 1951
3. Unger, A. H., and Unger, L. Annals of Allergy (March-April) 1952

For additional information just send your Rx Blank marked 7SP9.

Brewer EST. 1852

BREWER & COMPANY, INC. Worcester, Mass.

Pharmaceutical Chemists • Established 1852

when
endocrine
readjustment
is
a key
to
well-being

Pfizer

Syntex

you can now specify Pfizer Syntex oral, transmucosal and injectable preparations of androgens, estrogens, progesterone and combinations widely useful in practice today

Arrangements recently completed between the Pfizer and Syntex organizations now make possible a complete line of steroid hormone preparations available from PFIZER LABORATORIES. On the facing page are listed the initial groups of Pfizer Syntex preparations you can now specify, including Neodrol,* the newest agent for anabolic effect and tumor-suppression in selected cases with minimal virilizing side effects.

Research, discovery, development and wide clinical acceptance have distinguished Pfizer antibiotic agents, so often the choice of physicians in the control of infectious disease. The scientific research facilities and production controls of both Pfizer and Syntex assure the unsurpassed purity, potency and clinical excellence of the steroid hormone preparations supplied by PFIZER LABORATORIES.

Additional information on these specialties and their roles in your practice may be obtained by writing directly to Medical Service Department, PFIZER LABORATORIES, Division, Chas. Pfizer & Co., Inc., 630 Flushing Avenue, Brooklyn 6, N. Y.

*TRADEMARK

Pfizer

SYNANDROTABS®	Methyl Testosterone, U.S.P., Tablets 10 mg. and 25 mg.
SYNANDRETS®	Testosterone, U.S.P., Transmucosal Tablets 10 mg. and 25 mg.
SYNANDROL®	Testosterone Propionate, U.S.P., in Sesame Oil 25 mg., 50 mg. and 100 mg. per cc.; in single-dose disposable STERAJECT® cartridges and in 10 cc. multiple-dose vials
SYNANDROL®-F	Testosterone, U.S.P., in Aqueous Suspension 25 mg., 50 mg. and 100 mg. per cc.; in 10 cc. multiple-dose vials
DIOGYNETS®	Estradiol, U.S.P., Transmucosal Tablets 0.125 mg., 0.25 mg. and 1.0 mg.
DIOGYN®-E	Ethinyl Estradiol Tablets 0.02 mg., 0.05 mg. and 0.5 mg.
DIOGYN®	Estradiol, U.S.P., in Aqueous Suspension 0.25 mg. and 1.0 mg. per cc.; in single-dose disposable STERAJECT cartridges and in 10 cc. multiple-dose vials
DIOGYN®-B	Estradiol Benzoate, U.S.P., in Sesame Oil 0.33 mg. and 1.0 mg. per cc.; in 10 cc. multiple-dose vials
ESTRONE	Estrone, U.S.P., in Aqueous Suspension 2 mg. and 5 mg. per cc.; in 10 cc. multiple-dose vials
SYNGESTROTABS®	Ethisterone, U.S.P., Tablets 10 mg., 25 mg. and 50 mg.
SYNGESTRETS®	Progesterone, U.S.P., Transmucosal Tablets 10 mg., 20 mg. and 50 mg.
SYNGESTERONE® IN SESAME OIL	Progesterone, U.S.P., in Sesame Oil 10 mg., 25 mg., 50 mg. and 100 mg. per cc.; in single-dose disposable STERAJECT cartridges and in 10 cc. multiple-dose vials
SYNGESTERONE® IN AQUEOUS SUSPENSION	Progesterone, U.S.P., in Aqueous Suspension 25 mg. and 50 mg. per cc.; in 10 cc. multiple-dose vials
COMBANDRIN®	Estradiol Benzoate, U.S.P., 1 mg. and Testosterone Propionate, U.S.P., in Sesame Oil 20 mg. per cc. In single-dose disposable STERAJECT cartridges and in 10 cc. multiple-dose vials
COMBANDRETS®	Estradiol, U.S.P., 1 mg. and Testosterone, U.S.P., 10 mg. per Transmucosal Tablet
NEODROL®	Stanolone in Aqueous Suspension 50 mg. per cc.; in 10 cc. multiple-dose vials

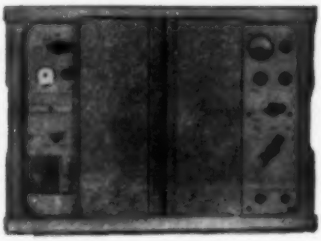
®TRADEMARK

PFIZER LABORATORIES
DIVISION, CHAS. PFIZER & CO., INC.

Brooklyn 6, New York

NOW... your choice

of 30 leads with General Electric's "DWB" Cardioscribe



The new GE Cardioscribe offers you the widest range of diagnostic flexibility and speed ever achieved. Yes, you can now get 30 different leads, including six chest positions, without changing the patient's electrodes — merely by turning selector switches.

Other design advances include self-stabilization for line-voltage fluctuations, which frequently cause unreadable tracings. And stabilization time between leads has been cut, facilitating exercise tests. You'll also like the improved paper drive. Independent of the stylus, it's easily loaded, can be adjusted for desired paper tension.

Ask your GE x-ray representative to show you these and many other feature advantages of the new GE Cardioscribe. You can also get complete information by writing X-Ray Department, General Electric Company, Milwaukee 1, Wisconsin, for Pub. M-9.

GENERAL ELECTRIC

To accelerate recovery in the common anemias

"Bemotinic" *liquid and capsules*

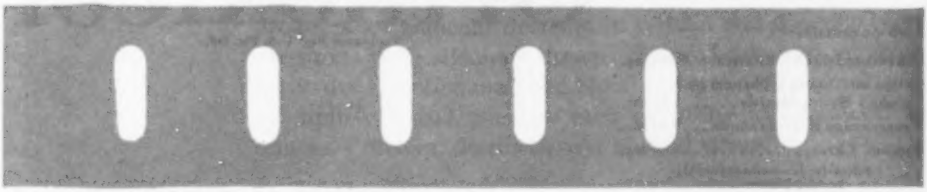
These two dosage forms provide essential factors – including a B_{12} potentiator – for maximal hemopoietic and clinical response.

"Bemotinic" Liquid – Unequalled for taste – pleasantly rich orange-flavor with no aftertaste – no need to dilute or mask – smooth, nonviscous, easy pouring – nonalcoholic.

Each teaspoonful (5 cc.) contains:

Ferric ammonium citrate	200.0 mg.	Folic acid	0.33 mg.
Vitamin B_{12} U.S.P. (crystalline)	4.0 mcg.	Thiamine HCl (B_1)	1.5 mg.
Extractive as obtained from of fresh gastric tissue	450.0 mg.	Riboflavin (B_2)	1.0 mg.
		Pyridoxine HCl (B_6)	0.2 mg.

Suggested Dosage: Adults: 1 to 2 teaspoonfuls. Children: ½ to 1 teaspoonful. Three times daily, or more as required. Preferably taken with food. No. 940 – Supplied in bottles of 16 fluidounces and 1 gallon.



"Bemotinic" Capsules

Each capsule contains:

Ferrous sulfate exsic. (3 gr.)	200.0 mg.	Desiccated liver substance, N.F.	100.0 mg.
Vitamin B_{12} U.S.P. (crystalline)	10.0 mcg.	Folic acid	0.67 mg.
Gastric mucosa (dried)	100.0 mg.	Thiamine HCl (B_1)	10.0 mg.
		Vitamin C (ascorbic acid)	50.0 mg.

Suggested Dosage: 1 or 2 capsules three times daily, or as directed by the physician. Preferably taken with food. No. 340 – Bottles of 100 and 1,000.

Ayerst

Ayerst, McKenna & Harrison Limited • New York, N. Y. • Montreal, Canada

Upjohn

cough control plus bronchodilatation:

Orthoxicol

Trademark Reg. U.S. Pat. Off.

Each cc. contains:

Dihydrocodeinone Bitartrate 0.365 mg.
Orthoxine (methoxyphenamine,* Upjohn) Hydrochloride ..... 3.38 mg.
Hyoscyamine Hydrobromide ... 0.02 mg.
Sodium Citrate ..... 65.0 mg.

*Beta-(ortho-methoxyphenyl)-isopropyl-methylamine

Available in pint and gallon bottles

The Upjohn Company, Kalamazoo, Michigan

An important new preparation . . . clinically accepted . . . for lowering blood pressure in both benign and malignant HYPERTENSION

VERALBA*

[Brand of Protoveratrines A and B . . . chemically standardized by an original Pitman-Moore assay.(6)]

(1) Crumpton, C. W. et al.: J. Pharm. & Exper. Therap., 106:378 (Dec.) 1952. (2) Currens, J. H. et al.: Abstract, Program American Heart Assn., April 18-19, 1952. (3) Meilman, E., and Krayer, O.: Circulation 6:212 (Aug.) 1952. (4) Hoobler, S. W. et al.: Ann. Internal Med., 37:465 (Sept.) 1952. (5) Smirk, F. H., and Chapman, O. W.: Am. Heart J., 43:586 (April) 1952. (6) Nash, H. A., and Brooker, R. M.: J. Am. Chem. Soc. 75:1942, 1953.

Recent clinical investigations(1-5) show that protoveratrine produces a significant decrease in systolic and diastolic blood pressures. With adequate dosage, this well-tolerated veratrum derivative can often maintain blood pressure near normal levels indefinitely,(2) and alleviate such symptoms as headache, insomnia, delirium, dizziness, and blurred vision.

The effective dose of protoveratrine for the individual patient can usually be readily established with Veralba Tablets. Their *chemically-standardized* protoveratrine content is *highly constant in potency* . . . permitting the careful estimation of dosage essential for optimal results from protoveratrine therapy.

Veralba is supplied as 0.2 mg. and 0.5 mg. grooved tablets, in bottles of 100.

*Trademark

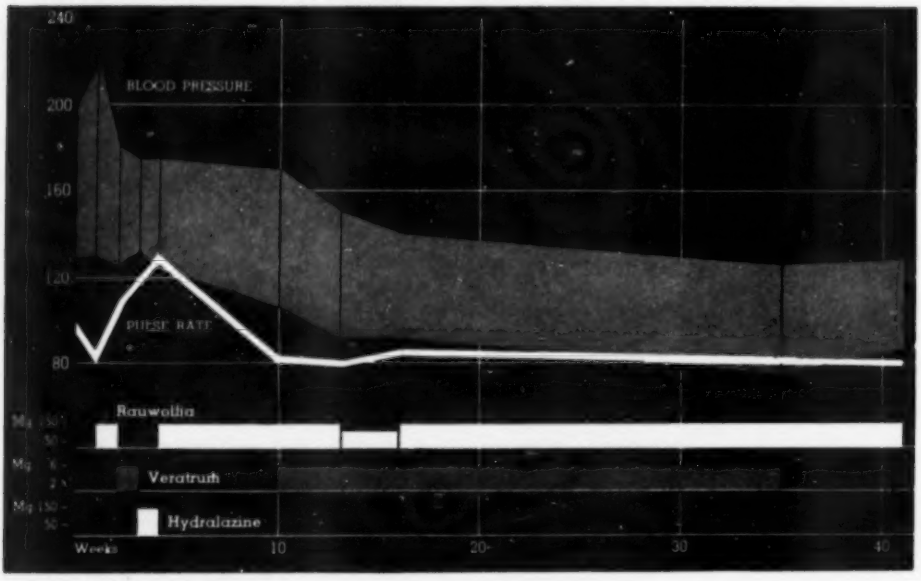
PITMAN-MOORE COMPANY

Pharmaceutical and biological chemists
INDIANAPOLIS 6, INDIANA
Division of Allied Laboratories, Inc.

Every patient with essential hypertension is a potential candidate for Raudixin therapy

Because of its safety and the stability of its hypotensive effect, Raudixin can be confidently prescribed for all patients with essential hypertension. It is especially recommended for the large, indeterminate group whose symptoms are not severe enough to warrant the use of other hypotensive agents. Critical adjustment of dosage is unnecessary.

In more advanced cases, Raudixin is a valuable adjunct to other agents.



This patient's blood pressure was lowered about the same amount by rauwolfia, veratrum or hydralazine. Hydralazine, however, caused undesirable reactions and increased the pulse rate. Veratrum augmented the effect of rauwolfia; and the effect was maintained even when veratrum was discontinued some months later. — After R. W. Wilkins, Ann. Int. Med. 37: 1144, 1952.

RAUDIXIN

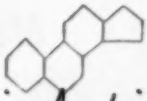
Squibb Rauwolfia

50 mg. tablets, bottles of 100 and 1000

Raudixin contains the whole powdered root of Rauwolfia serpentina. The wide clinical experience to date still makes the whole crude root the preferred form of the drug.

"RAUDIXIN" IS A TRADEMARK **SQUIBB**

cortisone + SCHERING = Cortogen

the symbol SCHERING denotes leadership in steroid hormone  research and manufacture -- including Cortogen in the most useful clinical forms. For systemic therapy, use Cortogen tablets or injection . For eye disorders use Cortogen ophthalmic suspension -- sterile . The Schering seal SCHERING appears on each tablet and package -- your assurance of quality.

CORTOGEN®

Acetate (cortisone acetate, Schering) Tablets, 5 mg. and 25 mg.;
Injection, 25 mg. per cc., 10 cc. multiple-dose vials;
Ophthalmic Suspension—*Sterile*, 0.5% and 2.5%, 5 cc. dropper bottles.

Schering CORPORATION · BLOOMFIELD, NEW JERSEY
In Canada: Schering Corporation, Ltd., Montreal

CORTOGEN

SCHERING

Bentyl *proves more effective than atropine in "Nervous*

The Wm. S. Merrell Company . . . *Pioneer in Medicine*

Indigestion"

McHardy[1] reports that Bentyl is "superior to atropine" for relief of pain due to pylorospasm. He confirms the work of others that Bentyl is free from significant side effects which permits more general use in nervous indigestion.

When you prescribe Bentyl, you prescribe patient comfort. You will rarely hear patients complain about "belladonna backfire" or dry mouth and blurred vision. Use Bentyl for your next nervous indigestion patient. Relief of G.I. spasm is quick, complete and comfortable.

Bentyl

An exclusive development of Merrell Research

New technic of measuring human motility shows a decrease or complete suppression of intestinal pressure waves, depending on dosage of Bentyl.[2] Bentyl acts by blocking acetylcholine and directly affects the muscle fibers like papaverine.

COMPOSITION: Each Bentyl Capsule or teaspoonful *Bentyl Syrup* contains 10 mg. Bentyl (dicyclomine) Hydrochloride.

Also *Bentyl* (10 mg.) *with Phenobarbital* (15 mg.) *Capsules and Syrup*, and *Bentyl Injection*, 10 mg. per cc.

DOSAGE: Prescribe Bentyl, 2 capsules or 2 teaspoonfuls Bentyl Syrup three times daily and at bedtime. Infants and Children, ½ to 1 teaspoonful Syrup 10 to 15 minutes before feeding. Three times daily.

1. McHardy and Browne: Sou. M.J. 45:1139, 1952.

2. Lorber and Shay: Fed. Proc. 12:90, 1953.

Complete Bentyl bibliography on request.

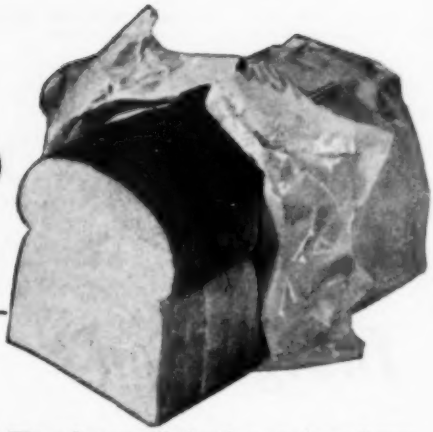
T.M. 'Bentyl'

for 125 Years

New York
CINCINNATI
St. Thomas, Ontario

Merrell
SINCE 1828

what does BREAD *contribute?*



Some twelve years ago the baking industry began large-scale, nationwide commercial production of enriched breads. Today such breads represent about three-fourths or more of all the marketed white bread in the United States,[1] and rank high among the foods which contribute essential nutrients—in important amounts—at low cost—to the nutrition of the American people.[2]

It is not so long since deficiencies of certain B vitamins and iron were regarded as sufficiently widespread in the United States to merit serious attention. By providing broad distribution of these important nutrients in effective amounts, commercial enriched breads have contributed notably to reducing the incidence of these deficiencies,[1] as reported for instance among patients of charity clinics throughout the country.[3] It is authoritatively believed that the enrichment of bread has improved the health of a large segment of our population.[4]

Per pound, enriched breads today contribute—as required by government definition and standards of identity[5]—at least 1.1 mg. of thiamine, 0.7 mg. of riboflavin, 10 mg. of niacin, and 8 mg. of iron. Thus they are distinctly superior to homemade as well as bakers' white breads of former years.

Each pound of commercial enriched breads contributes also 39 Gm. of protein—wheat flour protein supplemented with milk protein—biologically applicable to the growth processes as well as to tissue maintenance.[2]

Another significant contribution of such breads is 400 mg. of calcium per pound.[6] Last not least, and rather to be praised than to be deprecated, is the low-cost contribution of calories which bread makes to energy needs.

The appended table shows the important amounts of six essential nutrients contributed by six ounces of marketed enriched breads. The table also shows the notable percentages of the National Research Council's recommended daily allowances this small amount of present-day enriched breads represent.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

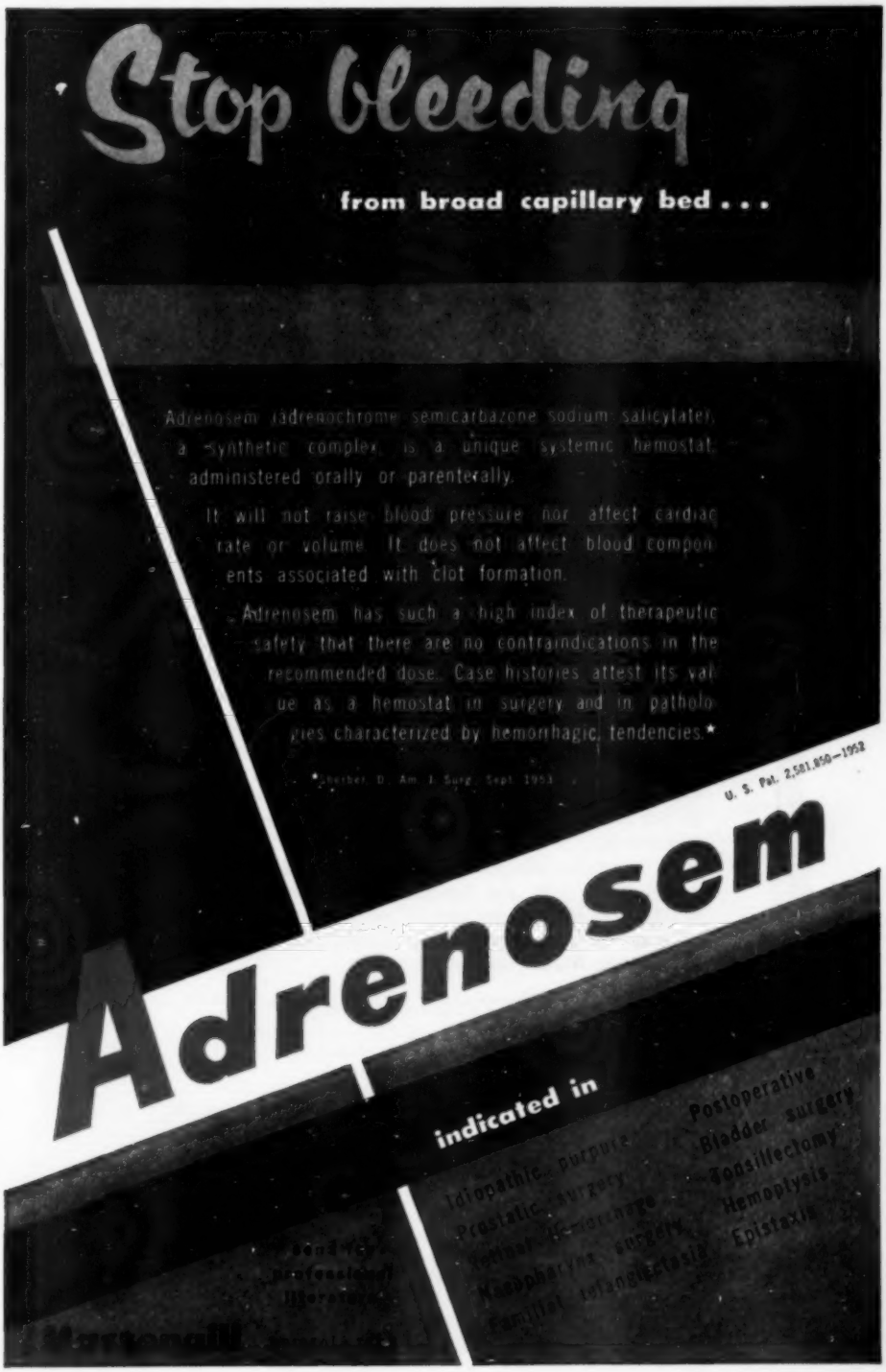
NUTRIENTS AND CALORIES CONTRIBUTED BY 6 OUNCES OF ENRICHED MARKET BREADS AND THEIR PERCENTAGES OF RECOMMENDED DAILY DIETARY ALLOWANCES*

Nutrients and Calories	Protein	Thiamine	Riboflavin	Niacin	Iron	Calcium	Calories
Amounts	14.5 Gm.[7]	0.41 mg.[7]	0.26 mg.[7]	3.8 mg.[7]	4.5 mg.[6]	150 mg.[6]	468[7]
Percentages of Allowances	21%	34%	14%	32%	38%	15%	20%

*Daily dietary allowances recommended by National Research Council for a sedentary man (154 lb.).

AMERICAN BAKERS ASSOCIATION
20 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS

1. Geddes, W.F.: Cereal Chemists Guard Nutrition, Agricultural and Food Chemistry *1*:38 (Apr.) 1953.
2. Sherman, H.C.: Chemistry of Food and Nutrition, ed. 8, New York, The Macmillan Company, 1952, pp. 597-600; 646.
3. Flour and Bread Enrichment, 1949-50: Prepared by The Committee on Cereals, Food and Nutrition Board, National Research Council, 1950.
4. Sherman, H.C.: The Nutritional Improvement of Life, New York, Columbia University Press, 1950, pp. 86-87.
5. Bakery Products; Definitions and Standards of Identity: Federal Register *17*:4453 (May 15) 1952.
6. Data furnished by the Laboratories of The American Institute of Baking, Chicago, Illinois.
7. Watt, B.K., and Merrill, A.L.: Composition of Foods—Raw, Processed, Prepared; United States Department of Agriculture Agriculture Handbook No. 8, 1950.


Stop bleeding
from broad capillary bed . . .
Adrenosem (adrenochrome semicarbazone sodium salicylate), a synthetic complex, is a unique systemic hemostat administered orally or parenterally.
It will not raise blood pressure nor affect cardiac rate or volume. It does not affect blood components associated with clot formation.
Adrenosem has such a high index of therapeutic safety that there are no contraindications in the recommended dose. Case histories attest its value as a hemostat in surgery and in pathologies characterized by hemorrhagic tendencies.*
*Archer D. Am. J. Surg. Sept. 1953
U. S. Pat. 2,581,850—1952
Adrenosem
indicated in
Idiopathic purpura
Prostatic surgery
Nasopharynx surgery
Familial telangiectasis
Postoperative
Bladder surgery
Tonsillectomy
Hemoptysis
Epistaxis

following anorectal surgery . . .

". . . more rapid postoperative healing as compared with patients on mineral oil"[1]

Cantor[1] concludes—after studying 400 patients, equally apportioned between mineral oil and refined psyllium therapy —that L.A. Formula accelerates healing as much as 2 to 4 weeks compared with patients taking mineral oil for the management of postoperative constipation following anorectal surgery. This is due, he states, to the clean wound area which L.A. Formula leaves for the better development of granulation tissue.

Cantor notes these additional advantages of L.A. Formula therapy. L.A. Formula provides an internal dilator action which acts to prevent adhesions, stricture and stenosis. Patients find L.A. Formula palatable and easy to take and do not become habituated to its use. Its laxative action is dependable.

He concludes that L.A. Formula "provides a natural, unabsorbable bulk and lubricant with no clinical disadvantages. It offers many advantages over mineral oil and has none of mineral oil's disadvantages." *Burton, Parsons & Company, Washington 9, D. C.*

Send for Samples for Clinical Appraisal

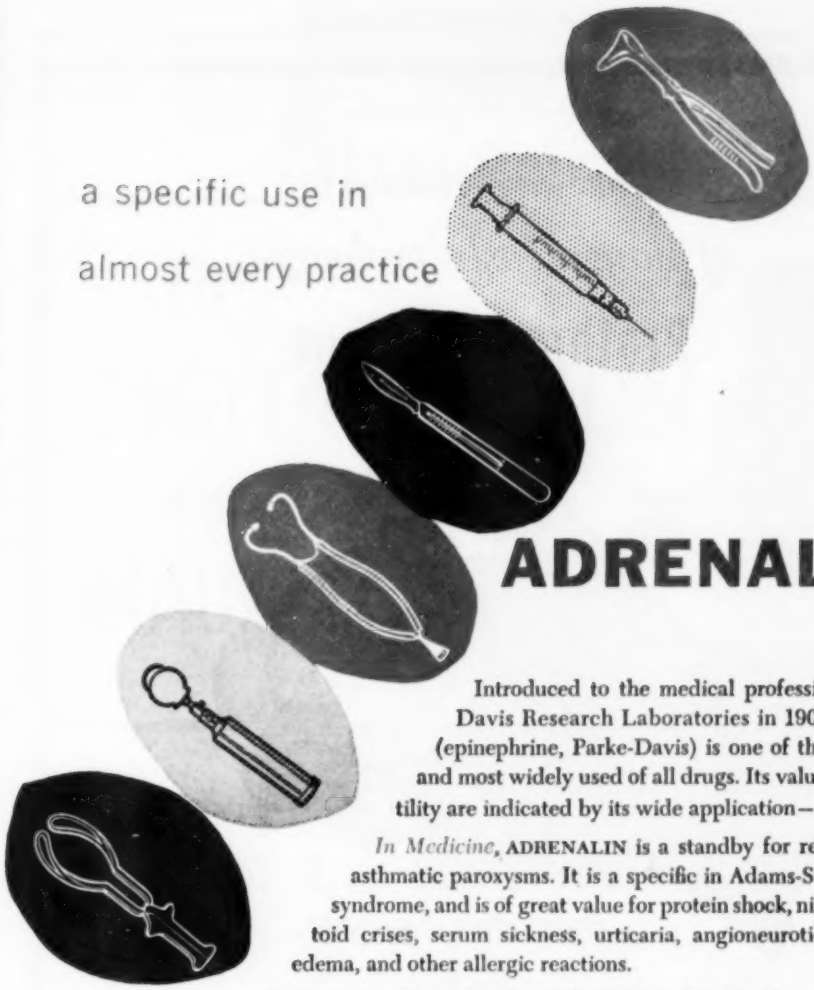
1. Cantor, A. J., Am. J. Proctol. 3:204-210, (Sept.) 1952.

L. A. FORMULA

effective bulk producer • unsurpassed for palatability

a specific use in

almost every practice



ADRENALIN®

Introduced to the medical profession by the Parke-Davis Research Laboratories in 1901, ADRENALIN (epinephrine, Parke-Davis) is one of the best known and most widely used of all drugs. Its value and versatility are indicated by its wide application—

In Medicine, ADRENALIN is a standby for relieving asthmatic paroxysms. It is a specific in Adams-Stokes syndrome, and is of great value for protein shock, nitritoid crises, serum sickness, urticaria, angioneurotic edema, and other allergic reactions.

In Surgery, ADRENALIN is employed to prolong local anesthesia by delaying absorption of the anesthetic agent, and to control hemorrhage.

In Obstetrics, ADRENALIN is used as a uterine relaxant.

In Anesthesiology, ADRENALIN is used to overcome cardiac arrest.

In Ophthalmology, ADRENALIN reduces intraocular pressure, vascular congestion, and conjunctival edema.

In Otolaryngology, ADRENALIN controls hemorrhage and provides prompt decongestion.

ADRENALIN is available as ADRENALIN Chloride Solution 1:1000, ADRENALIN Chloride Solution 1:100, ADRENALIN In Oil 1:500, ADRENALIN Ointment 1:1000, ADRENALIN Suppositories 1:1000, ADRENALIN Hypodermic Tablets 3/200 grain, and in a variety of other forms to meet medical and surgical requirements.

MEDICAMENTA VERA

Parke, Davis & Company

DETROIT, MICHIGAN

For sure reversal
of dangerously prolonged
Prothrombin Time

Prompt return to safe limits

MEPHYTON is the first fast-acting and unfailing antagonist for hypoprothrombinemia induced by Dicumarol® and other anticoagulants of this type. It has not been known to produce side effects when given as recommended. The action of MEPHYTON is detectable within minutes, and bleeding usually is terminated within 3 hours. Hypoprothrombinemia is reversed completely within 4 to 12 hours.

Literature on request

EMULSION OF
MEPHYTON
(Trade-mark)
(EMULSION OF VITAMIN K_1, MERCK)

Research and Production for the Nation's Health

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY

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LEAF ROUTE

To DIGITALIZATION AND MAINTENANCE

Pil. Digitalis (Davies, Rose)

0.1 Gram (approx. 1½ grains)

Physiologically Standardized

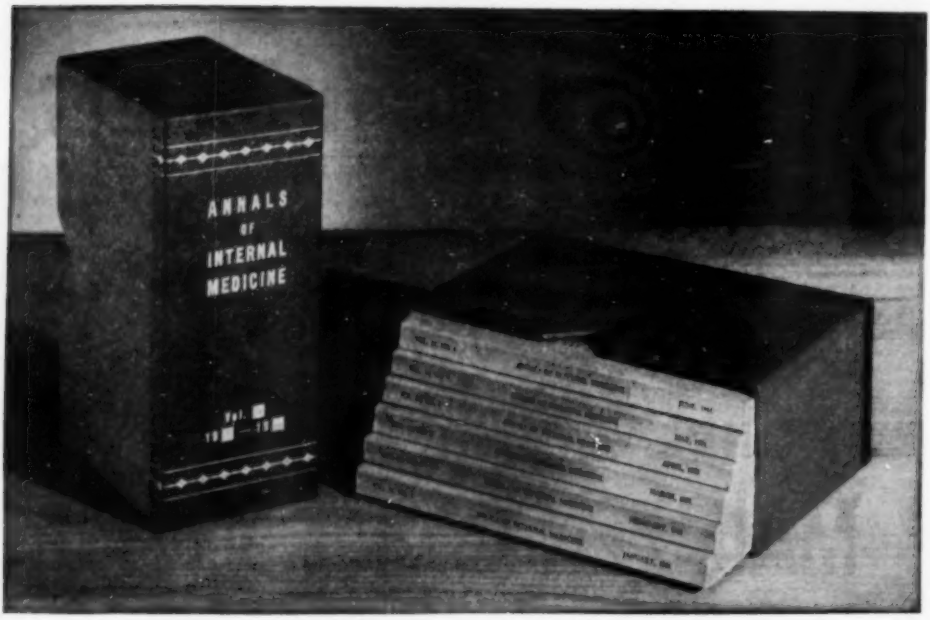
. . . provide the physician with an effective means of digitalizing the cardiac patient and of maintaining the necessary saturation

via the dependable "Davies, Rose" whole leaf route.

Clinical samples and literature sent to physicians on request

Davies, Rose & Company, Limited Boston 18, Mass.

PHARMACEUTICAL MANUFACTURERS D24



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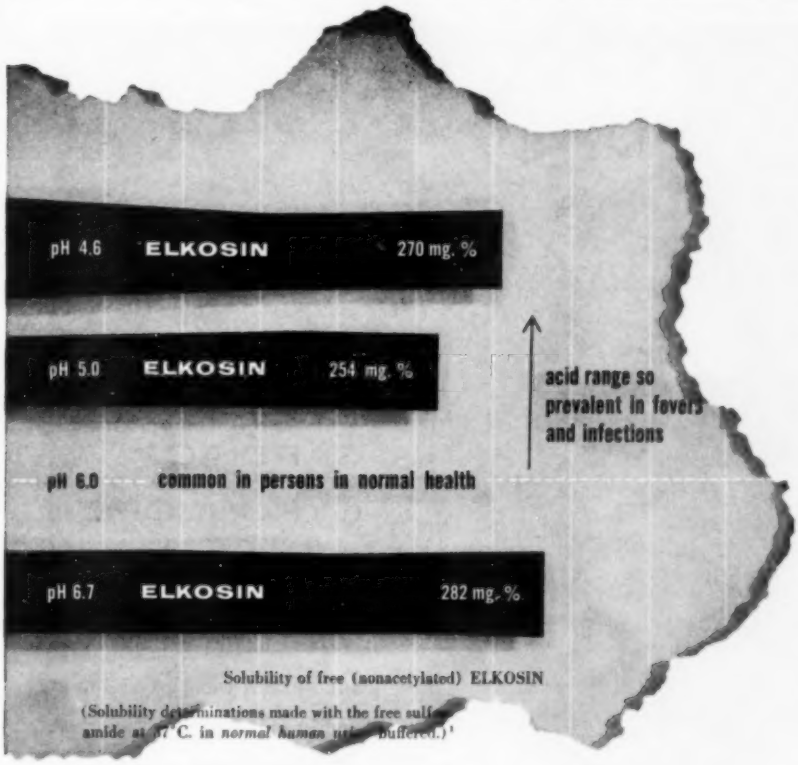
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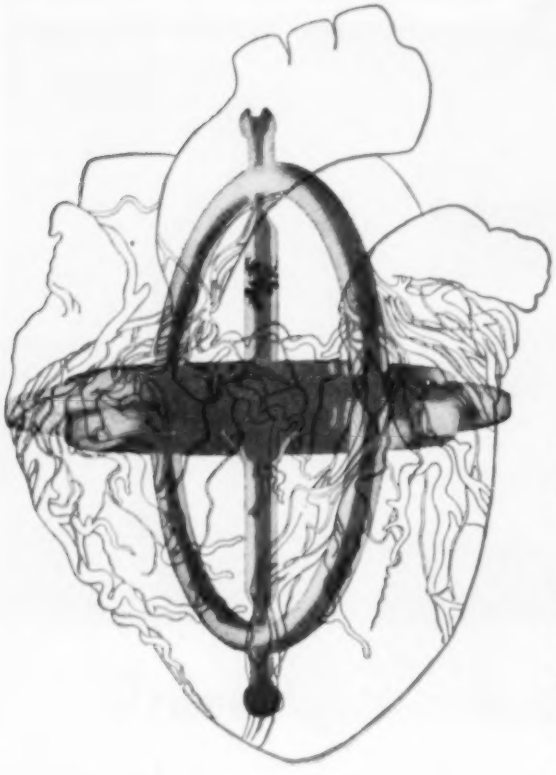

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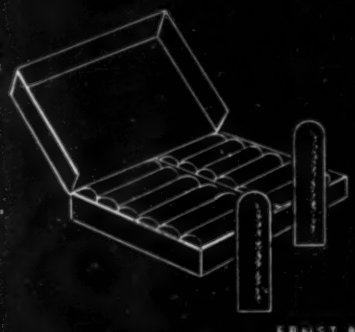

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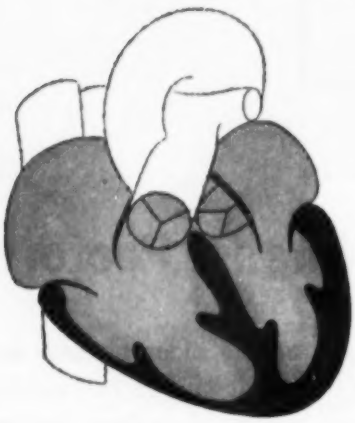

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ANNALS OF
INTERNAL MEDICINE

VOLUME 39 SEPTEMBER, 1953 NUMBER 3

ASPECTS OF THE ACTION OF INSULIN *

By CHARLES H. BEST, C.B.E., M.D., F.R.S., *Toronto, Canada*

THE award of the John Phillips Memorial Lectureship and Medal from this College has given me deep pleasure and great encouragement. I knew Dr. Phillips and therefore do not depend entirely on the statements of others in appreciating why you have perpetuated his name with these annual distinctions. John Phillips was a classmate in Medicine in Toronto with teachers, colleagues and close friends of mine—Drs. Edward Gallie, John Oille, George Wilson and the late Gerald FitzGerald.† John Oille won the Gold Medal when they were graduated 50 years ago this spring. John Phillips and George Wilson won Silver Medals. From the time I started my undergraduate clinical work I heard the praises of John Phillips sung by these distinguished members of his class and by many others of our Faculty. I am very proud indeed that my name has now been added to the list of those who have been chosen to give this lecture.

We have obviously passed the point of medical development at which an individual physician can truly qualify as a specialist in all branches of internal medicine. The clinical investigator must concentrate even more than the practising physician if he is to pinpoint his target, clearly visualize the problems, and advance knowledge of his special subject. The physiologist is, of course, also witnessing the division of his "country" into scores of "states," the boundaries of which are fixed by knowledge of technics as well as by scientific interest and capacity. I lecture to advanced students only on carbohydrate and fat metabolism, on blood clotting and thrombosis, and on certain aspects of endocrinology and nutrition, but it requires constant application and effort to keep abreast of the advances in these fields.

* Presented as the John Phillips Memorial Lecture at the Thirty-Fourth Annual Session of the American College of Physicians, Atlantic City, New Jersey, April 15, 1953.

† Professor W. E. Gallie, head of the Department of Surgery, University of Toronto, for many years; Dr. John Oille, dean of Canadian cardiologists; Dr. George Wilson, head of Surgery, St. Michael's Hospital, Toronto, for many years; Professor J. G. FitzGerald, founder of the Connaught Laboratories and School of Hygiene, University of Toronto.

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To plan, direct and do good research you *must* frequently think well ahead of existing knowledge. Occasionally it is known to everyone that a great goal has *not* been reached and the literature may be ignored, but the individual who follows this path more often attains oblivion than fame. When a real advance has been made it is a relatively short time before the weight of interest and ability of other laboratory groups force the originators to share or relinquish leadership. This is as it should be, and there will always be hosts of glittering new problems for those who can never be completely happy unless they are venturing into some phase of the unknown. It is more exciting to tackle a problem and, if fortunate, to enjoy for even a brief space the thrill of a new trail, than to develop well-established fields—but the latter course may be much more productive. As long as an investigator can continue to attract young minds and to keep his own open to the myriad opportunities which lie ahead in research, there is scope—and hope—for him.

The broad subject I have chosen for this Lecture was selected more on the basis of keen interest than of comprehensive knowledge, and I will choose only a few parts of it for discussion. I have been deeply interested in the action of insulin for almost 32 years, and perhaps in part because of this I feel that it is a very important aspect of physiology. I am confirmed in this belief by the fact that many great medical research departments are concentrating their attention on this subject at present. The evidence is accumulating that insulin is a central anabolic hormone without which many of the building processes, sometimes attributed entirely to other hormones, cannot proceed at the physiologic rate. Indeed, this is self-evident when we recall the devastating catabolic effects of pancreatectomy in many species, their complete relief by insulin, and the fact that the loss of no other single hormone produces more widespread catabolic derangements.

It will not disturb me if this last statement is vigorously challenged. We all have our favorite hormones which we tend to call "primary," while labeling the one our friend in another laboratory is particularly interested in "secondary," "nondominant," "exerting a permissive action," etc. I am well aware of the derangements produced by adrenalectomy (although these animals may grow on a salt-rich diet), and by parathyroidectomy.

Lack of insulin produces a failure of fat, protein and carbohydrate formation and storage, a decreased oxidation of sugar and a derangement of phosphate and potassium metabolism with a loss of these substances, as well as sugar, nitrogen and ketones, from the body. There are, therefore, literally scores of fascinating points which I might select for discussion, but a little later I shall concentrate on the work in our department on the growth effects of insulin in animals deprived of the pituitary gland. The findings have considerable physiologic and clinical interest, but I shall preface a discussion of them with a brief general survey of certain rapid advances in broader aspects of our subject.

The Advancing Knowledge of Fat Metabolism and the Part Played by Insulin

A fundamental finding which serves as a backdrop against which other aspects of fat metabolism are viewed is the flux or interchange of fatty acids between different tissues which Schoenheimer and Rittenberg [1] revealed by the use of isotopic labeling. The fact that a saturated fatty acid may have a double bond introduced, i.e., become unsaturated, that the reverse of this process can also occur, that the length of the carbon chain can be shortened or lengthened by enzymatic processes in various tissues—these are basic matters of great importance. Superimposed on this flux are the mass migrations of fat molecules produced, for example, by alterations of hormonal balance, and penetrating through it are the processes by which the fatty acids are oxidized to provide energy and heat. When the source of insulin is removed there is a rapid disappearance of depot fat and a large accumulation in the liver. This was shown by von Mering and Minkowski in 1889. The reversal of this flow by insulin was established by the Toronto group in 1922.[2] Stetten and Boxer in 1944 [3] showed that one of the major metabolic defects in diabetes was the loss of the ability of the body to form fatty acids from dextrose. This was reduced to a small fraction of the normal value, which could be restored by treating the alloxan-diabetic rats with insulin. In the normal rabbit treated with insulin, the rate of lipogenesis was increased several fold.[4] Bloch and Kramer in 1948 [5] were the first to demonstrate an in vitro effect of insulin on fat formation. Liver slices incubated in the presence of labeled acetate show incorporation of the label into fatty acids, and this process is enhanced by insulin if pyruvate is present. Brady and Gurin [7] have greatly extended this work. The diabetic liver fails to respond to insulin in vitro,[7] but if the insulin is administered to the animal and the liver subsequently studied in vitro, lipogenic ability is restored.[8] In these diabetic livers the oxidative metabolism of pyruvate, lactate and fructose may be unaltered but CO_2 production from labeled glucose is greatly depressed.[9] Fat synthesis requires the presence of an active metabolism of glucose, and the dramatic action of insulin on the former may be a reflection of its effect on the latter rather than a direct and specific action on one or more of the enzymatic steps in fat synthesis. Indeed, the finding that livers from alloxan-diabetic rats fed a fructose-containing diet synthesize fatty acids at an approximately normal rate, i.e., similar to that in glucose-fed animals which had been given insulin, indicates that the lipogenic effect of insulin is linked with the utilization of sugar.[10] We used to believe that fat formation from sugar was largely, if not exclusively, a hepatic phenomenon, but the proof that labeled glucose can be converted to fatty acids in the kidney and in diaphragmatic muscle, in heart, mammary gland and in adipose tissue, establishes the extrahepatic synthesis of fat. Popjak and Beeckmans [11] have shown that labeled acetate is converted into fatty acids in the mucosa of the intestinal tract and in

the lungs as well as in the liver. It is still probable, however, that a large proportion of fat synthesis takes place in hepatic cells.

This is not the place to discuss the great extension of our knowledge of the mechanism of formation of ketone bodies that has been made possible by the use of isotopes.[12] The dramatic suppression of diabetic ketosis by insulin was established by the early Toronto work. This was certainly a decrease of ketone formation rather than increased utilization, as later evidence from the same laboratory showed, but just how this is linked up with the lipogenic action of insulin or its prevention of the flow of depot fat to the liver is not known.

We are particularly interested here in the effects of insulin, and the evidence abundantly establishes the fact that the formation of long chain fatty acids from labeled glucose and from labeled acetate, which may arise from either fat or carbohydrate breakdown, is strongly stimulated by insulin. I will emphasize again that the lipogenic effect is observed after pretreatment of normal or diabetic cats or rats with insulin, but it is not elicited by the addition of insulin directly to the liver slice from a diabetic animal. Insulin, therefore, either forms an essential complex or product or reaches a more strategic site when injected into the whole animal. The fact that insulin added in vitro to a tissue from a nondiabetic animal may be effective suggests that the insulin already present has established some type of "pathway." The livers of animals deprived of both pancreas and pituitary form fatty acids from acetate at nearly a normal rate, i.e., there is some pituitary factor which inhibits the insulin effect on lipogenesis in the intact animal.[13]

Thus we see that insulin has widespread effects on fat formation and mobilization: (a) It promotes lipogenesis from glucose and acetate in the liver and in many extrahepatic tissues. (b) It prevents the loss of depot fat and the accumulation of fatty deposits in the liver. (c) It suppresses ketosis by inhibiting the formation of ketone bodies. These very important effects of insulin on fat metabolism are probably closely interrelated, and all may be linked with its action on the oxidation of glucose.

The Action of Insulin in Promoting the Oxidation of Sugar and the Formation of Glycogen

Banting and I asked ourselves in the summer of 1921, "What happens to the sugar which leaves the blood under the influence of our pancreatic extract?" We knew well the failure of liver glycogen formation and the low R/Q of diabetes. As you all appreciate fully, these signs of the diabetic state are erased by insulin. I shall not review the literature, but shall emphasize the importance of some recent findings which brighten the scene by washing away the battered and bleached remains of earlier hypotheses and conclusions.

Many of us have consistently taught that insulin increases the oxidation

of sugar. The older evidence on which this conclusion was based is not convincing when viewed from our present heights, but new data secured with the help of labeled glucose do provide satisfactory proof. Villee and Hastings (1949) [14] found that insulin increased the oxidation of glucose as judged by the rate of appearance of the carbon label in the CO_2 formed by the isolated rat's diaphragm. Similar results in the same preparation have been reported by Sacks and Sinex,[15] who found that insulin increased the turnover of isotopic phosphorus in various phosphorus compounds, the deposition of C^{14} labeled glucose as glycogen, and the oxidation of this labeled glucose. The findings on isolated tissues have been extended in an interesting and convincing manner by Wick, Drury, Bancroft and MacKay [16] who, by perfusing C^{14} labeled glucose into eviscerated rabbits, were able to distinguish between the glucose which disappears and that which is oxidized. When insulin was given there was a large increase in the C^{14} of the expired air, i.e., an increase in the amount of glucose oxidized. The glucose which was not oxidized, i.e., the labeled carbon, was found in nonglucose water-soluble compounds with smaller amounts in glycogen, protein and fatty acids.

Feller, Chaikoff, Strisower and Searle [17] used C^{14} labeled glucose to provide a final answer to the question of glucose utilization after complete removal of insulin-producing tissue. The rate of utilization was reduced to half the normal value and was completely restored by giving insulin.

In studies utilizing catheterization of the hepatic vein in normal and diabetic human subjects, Bearn, Billing and Sherlock [18] have obtained evidence of decreased hepatic output of glucose after insulin in both normal and diabetic subjects. This could have been due to fat or glycogen formation, or to decreased formation of glucose from protein in the liver. This latter possibility was not favored by the authors. Evidence of increased peripheral utilization of glucose was also obtained—presumably increased oxidation and muscle glycogen formation.

The rat diaphragm in vitro was shown by Gemmill in 1940 [19] to synthesize extra glycogen from glucose in the presence of insulin. Nelson in 1944 [20] was the first to demonstrate the inhibiting effect on glycogen synthesis in this preparation of a prior injection of anterior pituitary extract. Studies on interhormonal relationships, using the diaphragm technic, have yielded very important results which cannot be discussed here. Krahl [21, 22] has provided an excellent review and interpretation of these findings. The isolated rat diaphragm does not exhibit an increased oxygen uptake when insulin is added, but this effect has been reported by Johnson and by Gourley [23] in the isolated extensor digitorum longus muscle of the same species.

There is a good deal of interest at present in the possibility, revived and strongly supported by Levine, Goldstein, Huddlestun and Klein,[24] that insulin exerts an effect favoring the transport of certain sugars across the

cellular membrane. The most recent contribution to this unsettled question is that of Mirsky, Haft and Perisutti,[25] who find in studies of the isolated diaphragm that insulin may influence the rate of entry of some sugars into the intracellular compartment but that this is not dependent on the molecular configuration of the sugar, as the previous authors had suggested. The importance of this problem is obviously very great, as many established effects of insulin might be produced simply by increased rate of entry of glucose into the cells. If this effect of insulin on cell permeability should be established, the mechanism of production—enzymatic or otherwise—will immediately attract many students of this subject.*

Insulin and Protein Metabolism

The successful removal of all the pancreas from the dog by von Mering and Minkowski provided the opportunity for Minkowski to demonstrate the increased excretion of nitrogen in the diabetic state. Similar findings were made in many clinical studies. In our first investigations of the effects of insulin on depancreatized dogs, urinary nitrogen was estimated and we always calculated the dextrose to nitrogen ratio. Some of the figures suggested a fall in nitrogen excretion after insulin, but the abolition of hyperglycemia and glycosuria and the dramatic clinical improvement of our truly moribund animals occupied all our attention for a time. The first clinical report on the use of insulin, published by Banting, Best, Collip, Campbell and Fletcher in the March, 1922, issue of the *Canadian Medical Association Journal*,[26] contained no figures for nitrogen excretion, but a subsequent one by Banting, Campbell and Fletcher [27] provided the first evidence, in any species, that insulin reduced the elevated nitrogen excretion characteristic of the diabetic state. The first comprehensive study of this problem in depancreatized dogs was published from Toronto in 1924 by F. N. Allan,[28] who is now President of The American Diabetes Association. He found a very definite reduction when insulin was provided. Janney and Shapiro in 1926 [29] noted a fall in blood urea and nonprotein nitrogen in human subjects given insulin. In the same year Tashiro [30] found a similar effect on blood urea and amino acids in rabbits. Luck, Morrison and Wilbur in 1928 [31] reported that insulin caused a sharp fall in blood amino acids in rabbits and rats and in normal young men. There was a controversy for some years over the rôle of the adrenal medulla in this insulin effect, but in recent years it has become clear that epinephrine is certainly not an essential mediator of this action. In a classic study by Mirsky et al.[32, 33] it was shown that insulin decreases the rate of protein catabolism in the nephrectomized dog. In eviscerated animals insulin inhibits the rise in blood amino

* Dr. R. Levine has recently informed me that in vitro studies in his laboratory and in C. R. Park's have provided further support for the increase by insulin of the permeability of cells to glucose. Even more recently a summary of Dr. Park's findings has appeared in the program of the 48th Annual Meeting of The American Society for Clinical Investigation.

acids and increases the utilization of exogenous amino acids. Frame and Russell,[34] Russell and Cappiello [35] and Ingle et al.[36] found that insulin decreased the rate and extent of the rise in blood amino acids in eviscerated rats and that adrenal demedullation did not influence the effect. This was not related to the blood sugar level and was proportionate to the dose of insulin. Chaikoff and Forker,[37] studying depancreatized dogs in a series of carefully controlled experiments, found a linear relation between insulin dose and nitrogen retention. Hoberman,[38] using glycine labeled with heavy nitrogen, concluded that in alloxan diabetes in rats there are both increased protein breakdown and depression of protein formation from amino acids. The evidence which Forker et al.[39] have recently secured using methionine labeled with S^{35} indicates that the "lesion" produced by lack of insulin relates to failure of protein formation rather than increased breakdown. Lotspeich [40] has presented evidence that insulin acts to accelerate synthesis of protein from free amino acids. A correlation was found between the rate at which the individual amino acids are removed from the blood and the relative molecular proportions of these same amino acids in skeletal muscle. The investigation of Luetscher [41] on the metabolism of amino acids in diabetes mellitus is the most satisfactory recent clinical study with which I am familiar.

Sinex, MacMullen and Hastings [42] found that insulin stimulated the incorporation of C^{14} labeled alanine into the protein of isolated rat diaphragm when no carbohydrate substrate was available. When sugar was present the insulin effect on the amino acid was not definite. Krahl [43] has recently reported that the incorporation of C^{14} labeled glycine into glutathione and into protein by rat liver slices is greatly reduced by loss of insulin-producing cells. Insulin restores the rate of incorporation to normal. Krahl presents data which support the conception that insulin stimulates peptide synthesis rather than inhibits breakdown.

F. D. W. Lukens has recently reviewed the evidence bearing on the interrelationship of the pituitary growth hormone (somatotropin) and insulin on nitrogen retention, and this will appear in Ciba Foundation and UNESCO publications. He has discussed the earlier findings of F. G. Young, Gaebler and Robinson and of others and has presented the studies conducted in his laboratory with Milman and DeMoor. The following two conclusions are selected for emphasis here.

1. *Insulin is essential to the protein anabolic activity of the growth hormone.* The literature records that Mirsky, Young, Gaebler, Lotspeich, Frame and Russell, and Lukens, in distinct investigations, have agreed that the presence of insulin is essential for the protein anabolic effect of somatotropin. Some years ago F. G. Young discussed the relationship of the growth effect of somatotropin to the secretory capacity of the islet cells in a very comprehensive paper.[44]

2. *An increased secretion of insulin apparently occurs in response to*

somatotropin in normal animals. When a diabetic animal, maintained on insulin to secure a normal nitrogen retention, was given somatotropin, the dose of insulin had to be increased several times to recover the normal level of nitrogen retention. It is difficult, though not impossible, to find any explanation of this except insulin liberation by somatotropin. There are many other findings which point in the same direction, but *no direct evidence is available.* Recent reports [45] that the absence of histologic changes indicating beta cell stimulation by somatotropin is evidence against increased liberation of insulin cannot be accepted, since R. E. Haist and his colleagues [46] find a large increase in islet cell volume after somatotropin without any structural changes in individual islet cells that are detectable by competent histologists.

Lukens and his colleagues have obtained evidence in Houssay cats that somatotropin, under certain conditions, may function as the *dominant* hormone in nitrogen metabolism and be independent of minor variations in the supply of insulin. Frame and Russell [34] reached somewhat similar conclusions in eviscerated rats.

Mr. James Salter and I have recently established the fact that insulin in the absence of somatotropin, i.e., in the completely hypophysectomized animal, can satisfy all accepted criteria and thus qualify as a growth hormone. The insulin-treated animals exhibit an increase in all the main body constituents and a very definite augmentation of skeletal growth. In the counterpart of this situation, when the pancreas is absent and the pituitary is intact, somatotropin causes a greater nitrogen loss and other purely catabolic effects. Thus, under certain conditions, perhaps under most conditions, insulin is the *essential* hormone for nitrogen storage.

These experiments, in which gradually increasing doses of slow-acting insulin were given to hypophysectomized animals, had not been made before. It is well known that animals after removal of the pituitary are very sensitive to insulin. They combine in one individual certain of the etiologic factors present in Simmonds' and Addison's diseases. They should have many features in common with the child whose anterior pituitary gland has been destroyed by new growth or surgically removed.

The figures for weight increase, nitrogen retention and widening of the epiphyses of our insulin-treated hypophysectomized animals are in press; it will suffice here to state that the growth rate of these organisms as judged by all three of these criteria may be very rapid. The insulin-treated animals eat much more food than the controls, which remain stationary in weight. We have seen that insulin causes stimulation of utilization of several food components. I shall not discuss here the mechanisms of its effect on appetite.

Several points of general significance are settled. An organism with a very low blood sugar and great sensitivity to insulin can be stimulated by insulin to fulfill all the essential criteria of growth in the absence of somatotropin. Mr. James Salter and Mr. Robin Lawrence, in complete

nitrogen-balance studies, have extended our knowledge of the profound effect which insulin exerts on this element in hypophysectomized animals. They have also found that cortisone prevents the growth effect of insulin on the epiphyseal discs in spite of an increased food consumption and increase in weight.

But there are scores of interesting studies to be made using insulin, with various combinations of other hormones, which will help to clarify the whole pattern of hormonal influence on growth.

In conclusion I must admit that, in findings of this type, the main attraction for me is not their physiologic and clinical significance but the light which they focus on the fascinating pathways of research which lie ahead.

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CLINICAL EVALUATION OF ISONIAZID*

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Since 1944, the mainstay in drug therapy of tuberculosis has been streptomycin. This drug, especially in combination with para-aminosalicylic acid (PAS) and when used in dosage schedules designed to delay the emergence of resistant strains of *Mycobacterium tuberculosis*, has revolutionized the course and the prognosis of pulmonary and extrapulmonary tuberculosis. Nevertheless, the obvious drawbacks of streptomycin, such as its production of neurotoxic symptoms, allergic reactions and bacterial resistance, have encouraged the search for other mycobactericidal agents. A recent advance has been the development of hydrazine derivatives of isonicotinic acid.

The most promising of these compounds is isonicotinic acid hydrazide, Isoniazid (INA), a simple, easily synthesized, highly soluble crystalline compound. This drug is distributed under many brand names, among which may be mentioned "Rimifon," "Nydrazid," "Cotinazin," "Dinacrin" and "Ditubin." An isopropyl derivative, "Marsilid," has been less widely used because of its lower bactericidal activity in vivo and greater toxicity.

Although animal and in vitro experiments have demonstrated an additive therapeutic effect of combinations of streptomycin and INA, it was felt that it would be worth while accumulating sufficient tuberculosis patients treated by INA alone to afford a basic comparison between the action of this new drug and the well known action of streptomycin. Accordingly, beginning in March, 1952, all suitable patients ill with tuberculosis admitted to the University Division Medical Service of Kings County Hospital were treated with INA alone. This experiment was continued for some five months, until over 60 patients had been observed for a minimum of three months of drug therapy. A "suitable" patient was one who was ill with active and potentially reversible exudative, caseating or cavernous lesions. It was not anticipated that the predominantly fibrous reaction of the "good chronic" would provide visible evidence of resolution under drug treatment. Except for this requirement of reversibility, our patients were not selected by age, race, sex, extent or duration of disease, or by the presence or absence of complications such as those attributable to alcoholism or diabetes.

When a patient was admitted to this study, a control period of three weeks of bed-rest without drug therapy was usually instituted. During this preliminary period the effect of previous drugs was dissipated (a minority had been given a few grams of streptomycin), bed-rest and its effects were

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evaluated, and gross abnormalities in diet were corrected. This control period was most useful in correctly allocating the credit for any defervescence or gain in weight between the two potent therapeutic measures being used: bed-rest and INA.

After a suitable control period, INA was given to each patient in daily doses of 3 to 4 mg. per kilogram, divided into three doses. If substantial gain in weight took place, the dose of INA was usually increased appropriately. No other therapeutic measure was used besides bed-rest.

Each patient received the usual diagnostic work-up on the wards of the University Division and was supervised while under treatment by medical residents assigned to the Service of Pulmonary Disease. Because of previous reports of anemia and nephropathy produced by these agents, frequent examinations of the blood and urine were made. Serial roentgenograms of the chest were made at frequent intervals, never less often than monthly. Examinations of the sputum were made biweekly, then once a month. The otolaryngologists performed indirect laryngoscopy and bronchoscopy where indicated.

It had been planned to treat each patient with INA for a minimum of three months after the control period. In some cases, however, the lack of improvement or even the progression of the disease made it unwise to follow this plan rigidly, and INA was discontinued, with the substitution of streptomycin and PAS. The direct comparison of these drugs thus afforded was of considerable interest, and these cases will be described in more detail.

Results

We feel that when dealing with the treatment of a chronic disease the attempt at therapy itself is prone to produce changes in mood varying from depression to marked euphoria. Many patients will be overly suggestible and will attempt to please their physicians by offering them encouraging results. Then, too, in tuberculosis, the element of boredom is not sufficiently appreciated as a powerful factor in the community life of a chronic disease hospital. Here, the exciting novelty of a new drug becomes a major diversion, and those patients "fortunate" enough to be included in the study group attempt by exaggerated claims of well being to justify their selection. We therefore tried to use rigidly objective criteria in evaluating any response and rejected such uncertain measurements as "increased strength," "decreased toxicity," "increased feeling of well being." The following criteria were used:

1. Time for fever to disappear.
2. Gain in weight.
3. Roentgenographic changes.

The greatest emphasis was placed upon the roentgenographic changes. At the completion of the study each patient's serial films were reviewed by the authors, and agreement was reached on a final evaluation. The changes were graded as:

Worse
No change
Slight improvement
Moderate improvement
Maximal improvement that could be expected.

Of the 61 cases finally included in this study, changes in the chest roentgenograms were graded as follows:

Worse	6	18 = 30%
No change	12	
Slight improvement	18	43 = 70%
Moderate improvement	11	
Maximal improvement	14	

Many of our patients were relatively afebrile during the period of observation, and others became afebrile during the preliminary control period. Of 30 patients who were febrile, 14 failed to defervesce under INA therapy, seven became afebrile within one month of treatment, six became afebrile within two months, and three became afebrile within three months.

Fifty patients gained a total of 577 pounds during three months, for an average gain of 11.4 pounds. This average is of little statistical value, as the extremes were a gain of 37 pounds and a loss of 16 pounds. Many patients gained weight during the control period at a rate equal to or greater than the gain while under treatment.

There was only a rough correlation between the amount of weight gain, the temperature response and the roentgenographic changes. For example, in one patient without fever who had gained 23 pounds, new exudative infiltrates appeared, while in a streptomycin-resistant patient with severe posthemoptoic deterioration, a remarkable clearing of the chest film was accompanied by only a four pound weight gain in three months.

The enormous variability of the tuberculous patients' response to INA can be illustrated by brief case descriptions:

Case Reports

Case 1 (figures 1 and 2). A 39 year old white male. Tuberculosis since 1947. Phrenic crush, 1949. Streptomycin, five months (80 gm.). This patient developed, while on streptomycin and PAS, a cavity 5 cm. in diameter in the right upper lobe and cavities of 2 and 3 cm. diameter in the left upper lobe. After three months on INA the cavities closed completely. The patient was afebrile and had gained 17 pounds.

Comment: This is INA at its best. Here is demonstrated a complete reversal of the "downhill" course typical of streptomycin-resistant cavitary tuberculosis. This result can hardly be bettered.

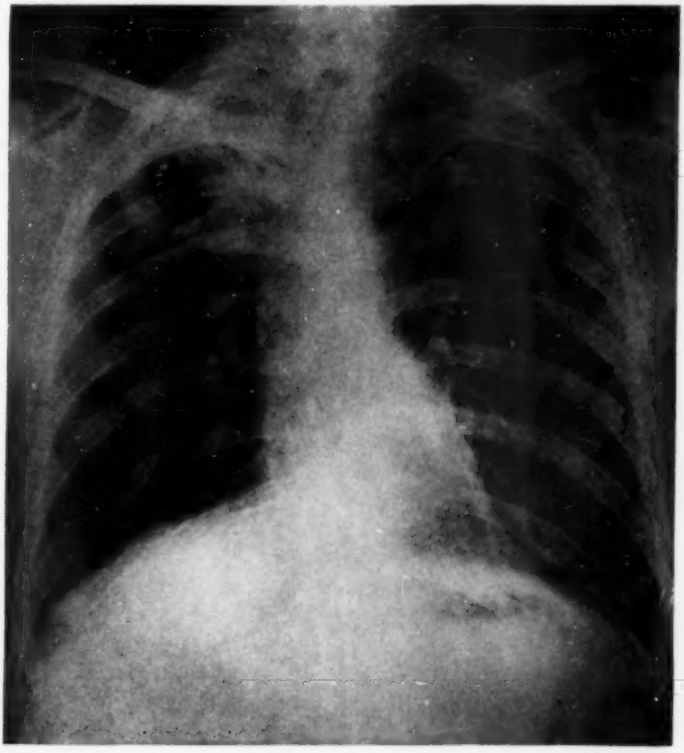

FIG. 1. *Case 1.* There is a 5 cm. cavity in the right first intercostal space, and a 2 cm. cavity in the left first intercostal space.

Case 2 (figures 3 and 4). A 47 year old white male. There was an acute onset of "pneumonia" six weeks before the beginning of treatment. The sputum was positive for tubercle bacilli and the temperature reached 101° F. There was atelectasis of the medial segment of the right middle lobe, with the demonstration bronchoscopically of endobronchial granulomata. With INA the sputum became negative for tubercle bacilli and the patient became afebrile in six weeks and gained 26 pounds. The atelectasis disappeared and two months later, on endoscopic examination, the bronchial mucosa was normal. After three months, slight fibrosis of the left upper lobe and a pleural cap of the right apex were the only residual abnormalities.

Comment: This case illustrated dramatic clearing of endobronchial disease by INA, with resultant clearing of atelectasis.

Case 3. A 17 year old Negro female. There was a gradual onset, two months before admission, of fever, cough and malaise. Large cervical nodes were found, with a widened mediastinum and hilar adenopathy. The sputum and a node biopsy were positive for *M. tuberculosis.* Exudative disease with "highlighting" of the right apex and the superior segment of the right lower lobe was present. After three months of INA there was but slight improvement of the exudative element in the lungs, with no obvious change in the nodes. The patient gained 37 pounds but fever persisted.

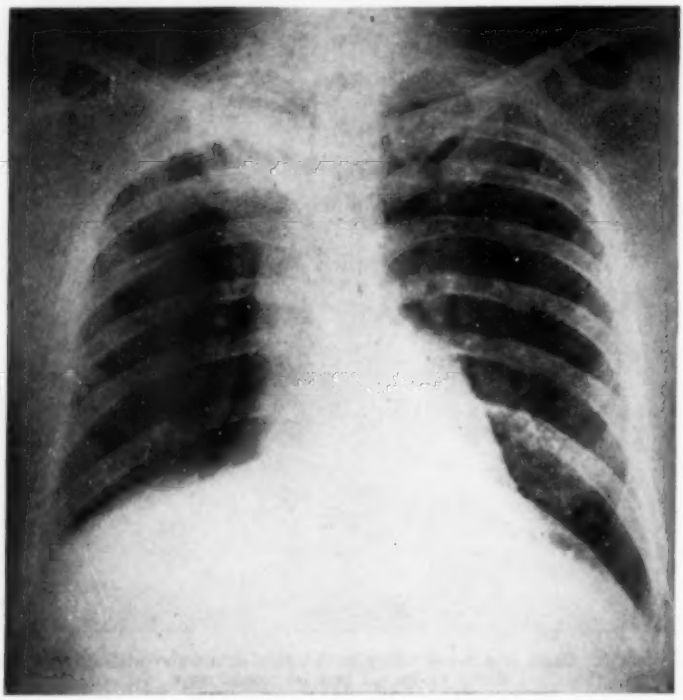

FIG. 2. *Case 1.* After three months' Isoniazid therapy, neither cavity can be seen.

Comment: The dissociation between the marked gain in weight and the therapeutic failure is striking. In such cases, streptomycin is ordinarily quite effective.

Case 4 (figures 5 and 6). A 33 year old Negro male. The onset was gradual, with cough, sweats, fever and loss of weight of three months' duration. The temperature was 101° F. and the sputum was positive. A cavity 4 cm. in diameter was present in the right upper lobe, with soft infiltrates in the right upper lobe and the left upper lobe. On INA, the patient became afebrile, sputum became negative for tubercle bacilli, and he gained 23 pounds. Although the cavity and the exudative

lesions in the left upper lobe disappeared, within two months fresh infiltration appeared in the left lower lobe, while full doses of INA were being given.

Comment: The healing of one set of lesions with the almost simultaneous appearance of fresh lesions points, seemingly, to infection with both INA-sensitive and INA-resistant bacteria. This case is representative of a group of similar responses to INA therapy.

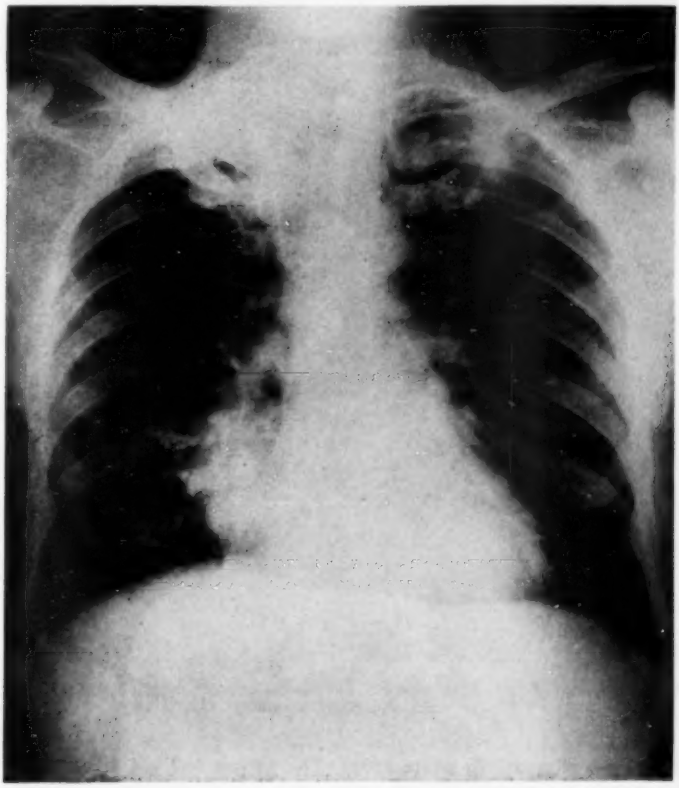

FIG. 3. *Case 2.* There are bilateral, essentially productive changes at both apices, with atelectasis of the medial segment of the right middle lobe.

Case 5. A 31 year old white male. There was a sudden onset of pleurisy. He was treated with streptomycin and PAS for seven months, with the development of resistance to streptomycin. Tuberculous laryngitis appeared and became painful enough to prevent swallowing, so that he was unable to eat. On INA, the larynx healed rapidly and the patient gained 14 pounds in three months. However, not only was the fever uncontrolled, but fresh pulmonary cavities developed while the patient was under INA therapy.

Comment: This is another example of the marked dissociation of drug response due to a mixture of INA-resistant and INA-sensitive strains, or due to differing organ response of the host to a single strain.

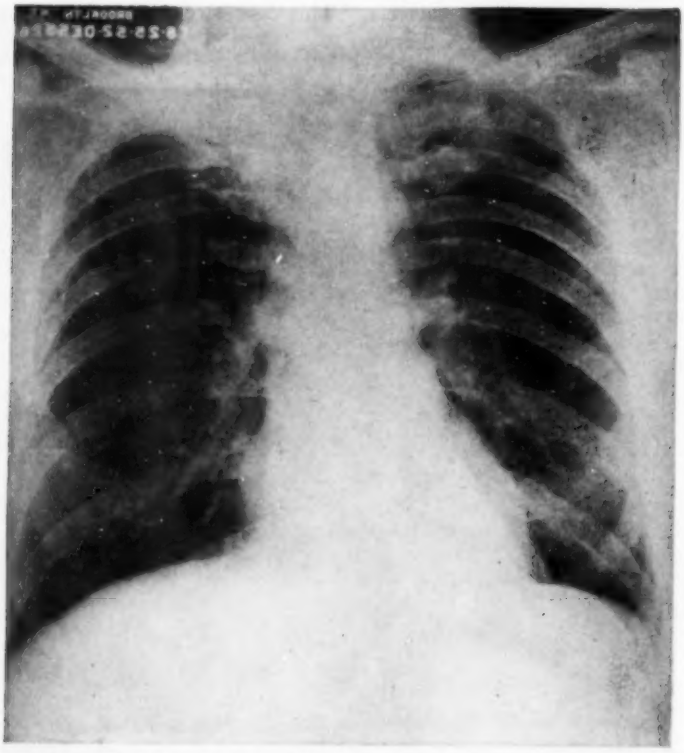

FIG. 4. *Case 2.* After three months' Isoniazid, there is complete reëxpansion of the atelectatic segment.

Case 6. A 68 year old white male. The patient had old apical scarring and caseopneumonic involvement of both upper lobes. A tuberculous epididymo-orchitis with a draining scrotal fistula was present. After three months of INA there was marked absorption of the pulmonary lesions but no improvement of the genital tuberculosis.

Comment: Here is another instance of a "therapeutic dissociation." The action of INA upon the lung was effective, but the action upon the genital lesion was nil.

Case 7 (figures 7, 8 and 9). A 30 year old Negro male entered with a fever of 104° F., bilateral epididymitis, vesiculitis, left orchitis and prostatitis. Obstructing

blood clots in the urethra and bladder produced acute urinary retention and an elevation of the blood urea. He had bilateral nodular pulmonary exudates. On INA there was marked genitourinary improvement, with lowering of the fever and the blood urea. After one month, however, fever returned to 104° F. and epididymo-orchitis recurred. There was a loss of one pound during this month, and the pulmonary lesions tended to become confluent. The pulmonary and genitourinary disease was subsequently controlled by streptomycin, with gain in weight and disappearance of fever.

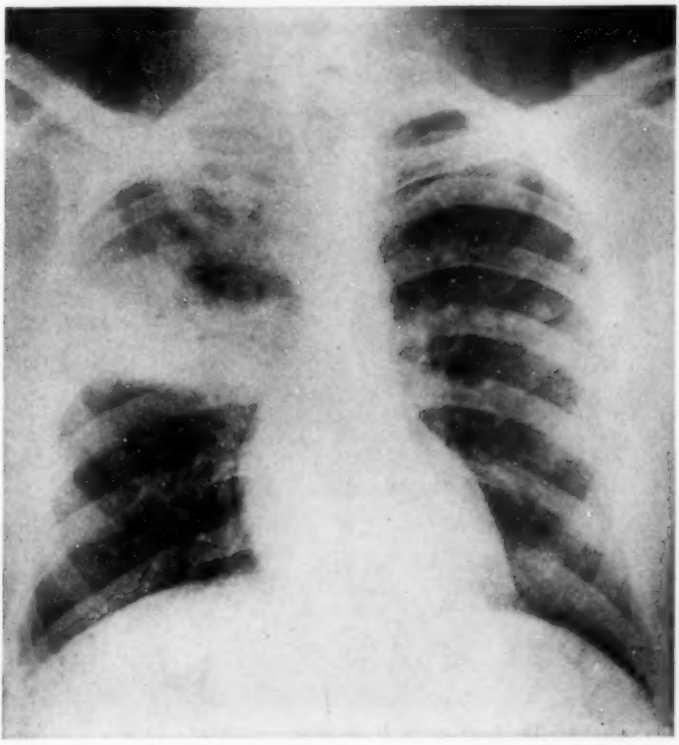

FIG. 5. *Case 4.* A 4 cm. cavity is present in the right upper lobe, with a large pneumonic area in the right midlung field. There are scattered exudative nodular lesions in the upper half of the left lung field.

Comment: This is an example of temporary control of genitourinary tuberculosis by INA, and then relapse (INA resistance). It is noteworthy that the pulmonary disease advanced while the genitourinary tuberculosis was improving.

Case 8. A 30 year old male Puerto Rican underwent left epididymectomy in January, 1950, for tuberculosis. He was admitted with an acute onset of right orchitis and epididymitis, with a fever of 102 to 104° F. His chest film was negative.

INA was given for three weeks without any response. Streptomycin and PAS were then given and there was prompt improvement.

Comment: This is a clear cut instance of failure of INA to act in a case where a favorable effect should have been obtained.

Our experience with three cases of acute miliary tuberculosis, one complicated by tuberculous meningitis, demonstrated a marked variability of action of INA:

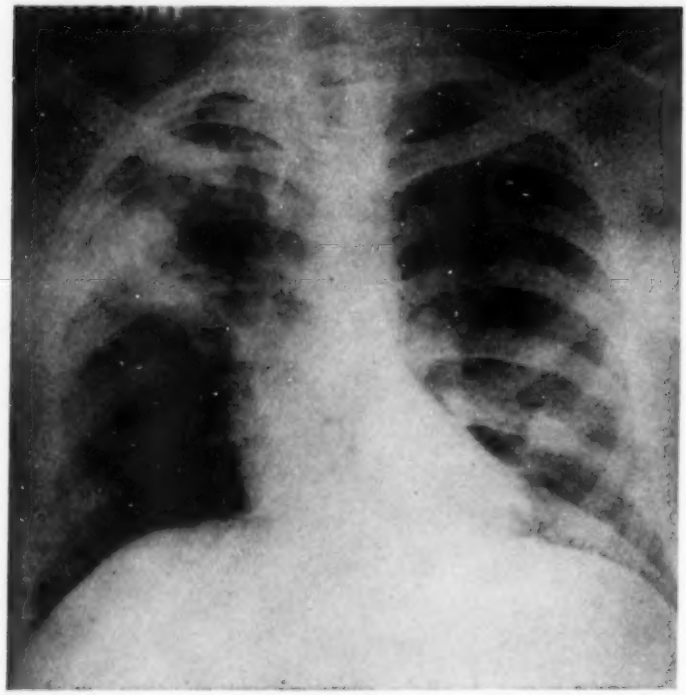

FIG. 6. *Case 4.* The large cavity is no longer visible, and there is moderate clearing of the pneumonic lesion. The exudative nodular lesions in the left upper lung field have also disappeared, but a new soft infiltrate has appeared in the left lower lung field.

Case 9. A 54 year old Negro female was admitted with a temperature of 104° F., tachypnea, prostration and classic miliary seeding of the lungs. After three and a half months on INA the fever was lower (100° F.), but the films were clearly worse and there was a further loss of 16 pounds. Streptomycin and PAS brought about prompt and complete recovery.

Case 10 (figures 10, 11 and 12). A 23 year old female Puerto Rican exhibited typical miliary lesions, fever of 103° F., tachypnea and prostration. After five weeks on INA (5 mg. per kilogram), patient was still febrile and obviously unimproved. After three months on streptomycin and PAS there was complete remission.

Case 11. An 18 year old Negro female had miliary tuberculosis and tuberculous meningitis. She was treated for three months with streptomycin by the intramuscular and intrathecal routes, together with oral PAS, with clearing of the pulmonary lesions and lowering of the temperature but with persistence of pleocytosis, depressed sugar and elevated protein of the cerebrospinal fluid, and nuchal rigidity. After three months of INA there was complete clinical and laboratory remission.

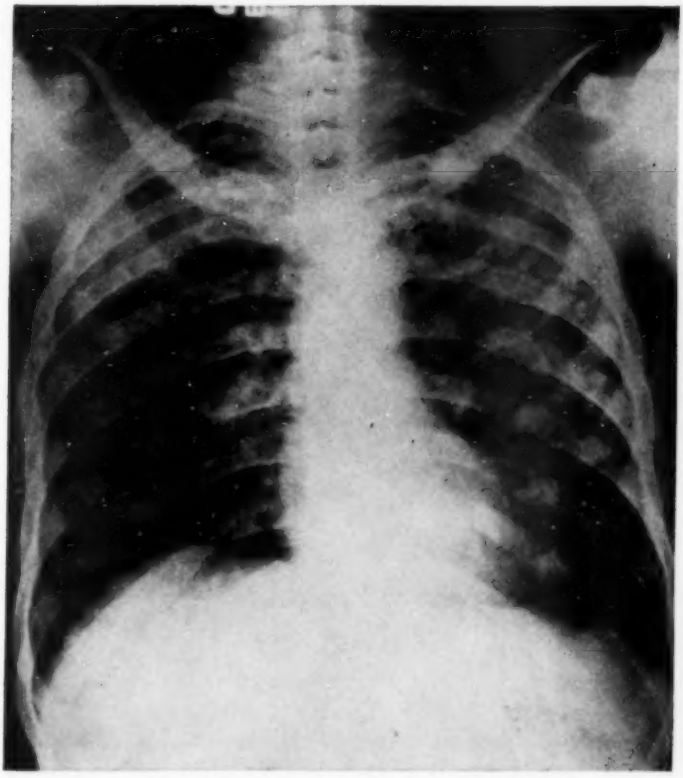

FIG. 7. *Case 7.* There is extensive bilateral caseocavernous disease.

These 11 cases demonstrate, better than statistics can, the great variation in response to INA of patients whose lesions seemed essentially similar. Results of INA treatment are apparently less certain and less predictable than results obtained with the use of streptomycin and PAS. At one extreme, rapid clearing of lesions and prompt arrest are seen, while at the other extreme, steady and unaltered progression of the disease occurs. Between these poles, all degrees of response form a virtual spectrum.

Discussion

There is no doubt that the INA group of drugs constitutes another effective antituberculosis agent. Controlled experiments, using varying doses and combinations of INA with other antibiotics, will eventually establish its definitive place in the therapy of tuberculosis. Some of these experiments have been reported in preliminary form and other experiments are in progress.

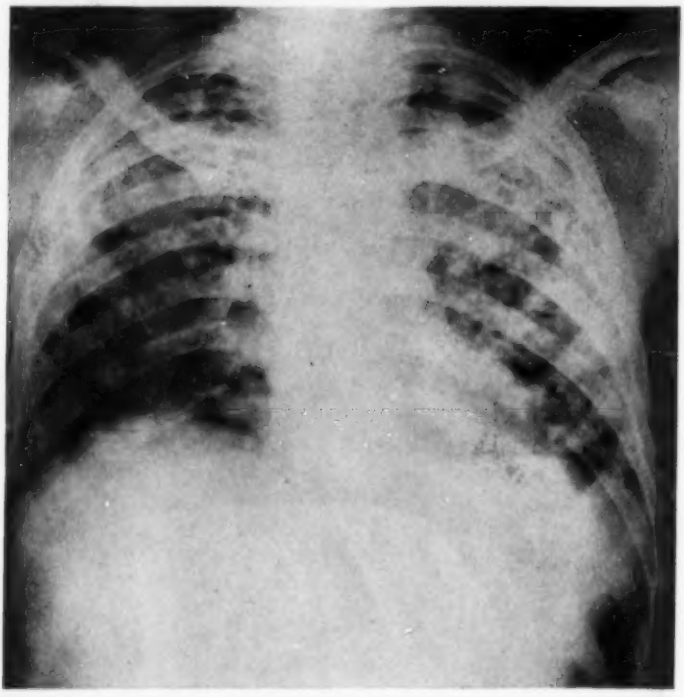

Fig. 8. *Case 7.* After one month of therapy with Isoniazid there is definite coalescence of the lesions, particularly in the left lung field.

This study has impressed us more with the similarities between INA and streptomycin than with any differences. Certain of these differences will be discussed in detail.

By now it is fairly well established that the combination of streptomycin in daily or in intermittent dosage, with PAS, will cause defervescence in the average case of acute uncomplicated pulmonary tuberculosis within two weeks. In comparison, the action of daily INA, in the dosage used by us, is neither so rapid nor so dependable. Almost half of our patients remained

febrile to some degree, and only a quarter became afebrile during the first month of therapy. When the INA cases who remained febrile were given streptomycin and PAS, the great majority promptly became afebrile. This less-than-perfect ability of INA to control fever seems at variance with early reports in which it was noted: "In some patients the temperature returned to normal in as few as two days; in others, 21 days were required. Almost all temperatures were normal by the tenth day of therapy." [1] However, in a later article [2] those authors report that 38 patients (of a total of

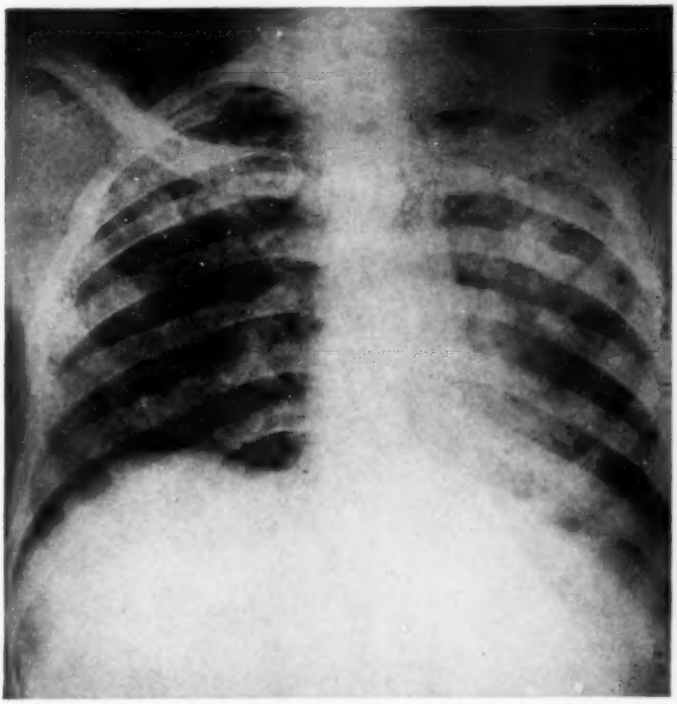

FIG. 9. *Case 7.* After two months of therapy with streptomycin and para-aminosalicylic acid there is moderate improvement.

65 treated with INA) were febrile or subfebrile after therapy. This amounts to 24 per cent "temperature failure." Presumably, if our rigid requirement for normal temperature (98.6° F.) had been adopted, their evaluation as to effects upon fever would be similar to ours.

Our study confirms other reports of substantial gain in weight in patients treated with INA. The gain in weight is greater in those who were most undernourished before entering the hospital. Many of our patients gained

weight during the control period at a rate often equal to or greater than the rate while receiving the drug. The gain in weight is of course due to bed-rest and a nutritious diet. Gains in patients being treated with INA are of the same magnitude as the gains in those treated with streptomycin. It should be stressed that gain in weight does not necessarily parallel therapeutic effects. A number of our patients have gained 20 to 30 pounds while demonstrable spread of their lesions was occurring. The converse was also observed.

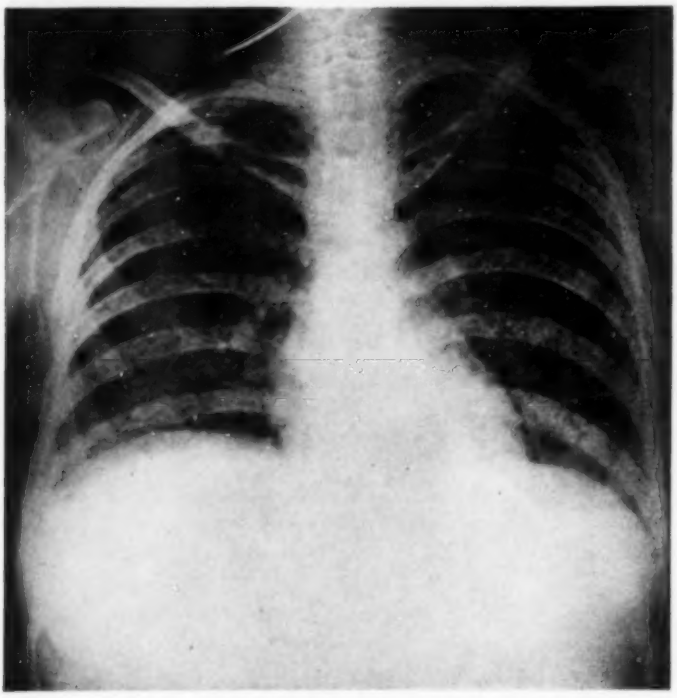

FIG. 10. *Case 10.* Typical appearance of miliary tuberculosis before commencement of therapy.

Our results, evaluated roentgenographically, are grouped for purposes of evaluation into two categories: satisfactory, 70 per cent; unsatisfactory, 30 per cent. There is but one comparable study,[2] and here, 61 per cent of the cases are classed as satisfactory and 39 per cent as unsatisfactory. Inasmuch as the bulk of our cases were potentially reversible, completely or in part, it is expected that our results would be somewhat superior to those obtained in a group of patients with extensive lesions, almost all of which

were previously unsuccessfully treated. It is therefore fair to say, from the available evidence, that about three fourths of patients initially treated with INA, in doses of 3 to 5 mg. per kilogram daily, will demonstrate some degree of roentgenographic improvement. Such results are inferior to those obtained in comparable patients treated with a combination of streptomycin intermittently with PAS daily.

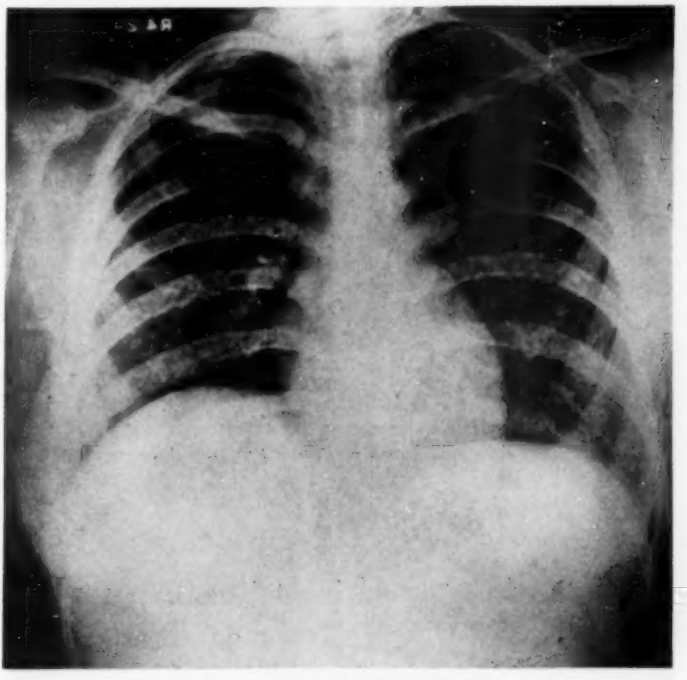

FIG. 11. *Case 10.* After therapy with Isoniazid (5 mg. per kilogram daily), little change is noted.

Roentgenograms of healed lesions in the pre-antibiotic era demonstrated, in a substantial number of cases, considerable fibrosis. Anatomic studies often revealed marked perifocal fibrosis, which is apparently responsible for much of the difficulty in pulmonary ventilation appearing in long-standing healed or arrested cases. An important advantage of therapy with streptomycin has been the prevention of much of this perifocal fibrous reaction. It is too soon to be certain, but from the appearance of the chest films of cases healed with INA we feel that this drug, too, will decrease the perifocal reaction.

In three patients ill with genitourinary tuberculosis (cases 6, 7 and 8),

INA was quite inferior to streptomycin, having no effect in two of them and but a transient effect in the third.

In one patient with glandular tuberculosis (case 3), INA had no appreciable effect upon the glandular infection.

Two patients suffering from miliary tuberculosis, treated with INA at 3 mg. per kilogram in one instance and at 5 mg. per kilogram in the other, were therapeutic failures but responded as expected to streptomycin and PAS (cases 9 and 10). One patient with miliary tuberculosis complicated

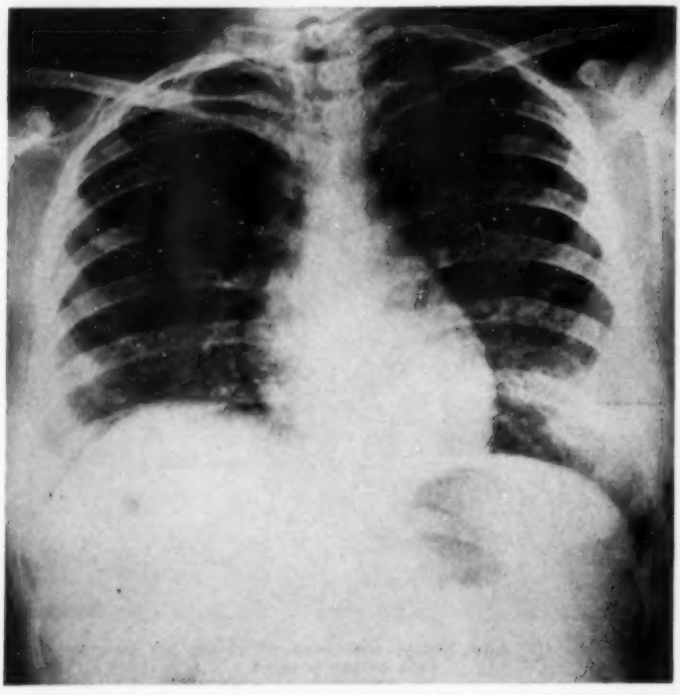

FIG. 12. *Case 10.* After treatment with streptomycin and para-aminosalicylic acid for two months, there is almost complete clearing of the miliary seeding.

by tuberculous meningitis (case 11) was studied. The lung lesion was successfully treated by streptomycin and PAS, and the meningitis was improved but not controlled. The addition of INA produced rapid improvement in the spinal fluid. Our patients are too few for adequate discussion, but the extensive experience of Clark and the New York Hospital group [8] is available for discussion. They have found that in miliary tuberculosis, patients treated with streptomycin and patients treated with INA (five to 10 mg. per kilogram daily) were essentially similar in rates of defervescence

and roentgenographic clearing. As Clark et al. point out, PAS was not combined with streptomycin in these patients. They draw no therapeutic inferences from their study of tuberculous meningitis. However, Nash and Grosfeld [4] state: "Except in tuberculous meningitis, in which we have found INA to be definitely superior to any drug we have used heretofore, we feel that streptomycin is still a better all-around antituberculosis agent."

This superiority in meningitis may be due to the potent intracellular activity of INA,[5] as well as to its superior diffusibility into the meninges.

Toxicity

A wide variety of side effects and toxic symptoms has been attributed to INA. Among these are constipation, postural hypotension, hyperreflexia and irritability, twitchings, slight anemia and occasional albuminuria. We found almost no toxic effects from INA at levels of 3 to 5 mg. per kilogram. Two patients stated that they felt "jittery," but after reassurance, and without change in the dose, their symptoms disappeared and did not return. In two additional patients there was a transient increase in fever and sputum, followed by improvement. This pattern was thought to resemble a Herxheimer reaction, an expression, perhaps, of rapid destruction of mycobacteria. A similar reaction is described by Dr. C. W. Bartley,[6] who does not necessarily follow our interpretation. No changes were noted in blood or urine, and none of the evidences of hypertonia of the autonomic nervous system mentioned by other investigators were encountered. In a smaller series of patients 7 to 10 mg. per kilogram daily were given for some weeks without evidence of toxicity. These observations confirm those of Elmendorf et al.[7] who noted no toxicity in a smaller number of patients. The package inserts enclosed by some manufacturers of INA caution against exceeding a daily total of 200 mg. We have used well over twice this amount on numerous occasions without causing overt toxicity. Unless unexpected long-term toxic effects appear, INA will be a well tolerated chemotherapeutic agent.

"Dissociated Action"

We have been impressed, in this study, with an apparent "dissociation" of therapeutic effect upon different lesions in the same patient. The loci of these lesions may be in the same organ or in different organs. Patient 3 is an example of partial clearing of lung lesions with no improvement in the infection in the lymph nodes. In patient 4 the lesions of the upper lobe cleared and remained healed, while new lesions of the lower lobe appeared. Similarly, in patient 4b (not described above), whose disease is almost identical with that of patient 4, a caseopneumonic infiltrate of the right upper lobe cleared while fresh exudation appeared in the right lower lobe.

In patient 5 severe tuberculous laryngitis and cavitary pulmonary disease were present. Organisms resistant to streptomycin were cultured from the sputum. After therapy with INA the laryngeal lesions healed promptly,

but fever continued and fresh pulmonary cavitations appeared. Patient 6 demonstrated clearing of exudative pulmonary disease while the genitourinary disease remained uncontrolled. Patient 7 is an example of temporary control of genitourinary tuberculosis. After one month apparent resistance to INA appeared. During this month, however, the nodular pulmonary exudates progressed to coalescence.

Marked variations of therapeutic effect may, of course, be due to anatomic differences. Tuberculosis varies in its behavior in a tubular organ such as the lung or kidney from its behavior in a solid organ such as the liver or spleen. While "old" lesions are disappearing under the influence of INA, the appearance of "new" lesions in another portion of the lung may be explained by minor anatomic variations, such as the opening or closing of a bronchiole, or the alteration of blood supply by thrombosis of a small vessel, or the alteration of lymph flow by inflammation or fibrosis of a draining lymph node.

To our minds, the more plausible explanation for such "dissociated" action is the assumption that many patients are infected with multiple strains of *M. tuberculosis*. Some of these strains are resistant to INA and others are sensitive. There is no way of determining quantitatively the proportions of either strain, and of course, without the use of INA, no clue even to the very existence of such strains appears. When INA is given a sharp reduction in the population sensitive to INA takes place which, in favorable cases, is sufficient to enable the host to control the remaining bacteria and produce arrest of the lesion. If one organ is infected by a higher proportion of resistant strains, the reduction of the bacterial population following treatment with INA may be insufficient to permit the host defense mechanism to achieve a cure. In such an instance the drug may fail to sterilize the lesion and may appear to have been a failure, in spite of a marked yet insufficient bacteriostatic effect. The interaction of anatomic and immunologic factors in different organs, with the seeding by chance of these organs with different ratios of resistant to sensitive strains of bacteria, is sufficient to explain the variations of response to INA seen in our patients.

There is as yet no direct evidence of multiple infections of human beings with INA sensitive and resistant strains of *M. tuberculosis*, but the analogous mixed infections with strains of organisms sensitive and resistant to streptomycin are well documented. A series of 24 lung specimens containing multiple lesions was described in the *Annales de l'Institute Pasteur*. In eight specimens, strains from different lesions exhibited the same degree of streptomycin resistance; in five specimens there were slight degrees of difference, and in 11 specimens there were real differences in the sensitivity of strains isolated from diverse lesions. As would be expected, the shorter the duration of treatment, the greater the degree of variations among the strains.[8]

We therefore visualize the tuberculous infection as consisting of the

action of antibiotics upon a heterogeneous population of numerous organisms with all degrees of sensitivity to streptomycin, INA, PAS, terramycin, viomycin and, indeed, to antibiotics as yet undiscovered. When any antibiotic is used and its effect noted on this mixed population, it appears possible then to classify the organism according to its sensitivity or resistance to the bacteriostatic effect of this antibiotic. Similarly, a second or third antibiotic which acted on another metabolic system in the tubercle bacillus would have a like effect on differentiating the sensitivity of the components of the bacterial population.

A therapeutic effect is noted when an antibiotic or a mixture of antibiotics exerts a bacteriostatic effect on the tubercle bacilli, thus permitting the defense mechanism of the host to become active in coping with the infection. Such a concept leads to the advisability of using together all therapeutic agents which possess a tuberculostatic action.

Summary

1. Isoniazid is an effective antituberculosis drug. In tuberculous meningitis it is probably superior to streptomycin. In caseocavernous pulmonary or extrapulmonary tuberculosis, INA is probably less effective than streptomycin.

2. The therapeutic response of basal pulmonary tuberculosis to INA is less dependable and more variable than to streptomycin and PAS.

3. Favorable radiographic changes were obtained in 70 per cent of the cases, unfavorable changes in 30 per cent.

4. Clinical evidence was obtained for the existence of a "dissociated therapeutic action" of INA. This dissociation consisted of simultaneous resolution of one lesion with progression of another. Illustrative cases are discussed.

5. At present, theoretic considerations strongly support the simultaneous use of streptomycin, PAS and INA.

Acknowledgment

Grateful acknowledgment is made to Dr. Perrin H. Long, Professor of Medicine, and his resident staff, Dr. Martin Metz, Dr. Murray Strober, Dr. Benjamin Rosenberg and Dr. Jacqueline Messite, for their aid and coöperation in carrying out this study.

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RESULTS FOLLOWING PULMONARY RESECTION OF TUBERCULOUS DISEASE WITH SPECIAL REFERENCE TO LOCALIZED NECROTIC LESIONS *

By James H. Forsee, Colonel, MC, F.A.C.P., Carl W. Tempel, Colonel, MC, F.A.C.P., and Edwin L. Scott, Major, MC, *Denver, Colorado*

Background Factors for Evaluating the Place of Resection in Pulmonary Tuberculosis

Pulmonary resection for active tuberculosis was seldom employed at Fitzsimons Army Hospital prior to the introduction of streptomycin; hence, follow-up studies must of necessity be limited to the period subsequent to 1946 (figure 1). A tenfold increase in the utilization of excisional surgery has occurred coincident with improvement of antituberculosis drug therapy and surgical technic during the past six years.

Included in this report are those patients proved to have tuberculosis before operation, and those who submitted to thoracotomy primarily for diagnosis and then continued on treatment after the excised lesion was judged to be tuberculous. It is not within the scope of this paper to discuss the diagnostic aspect of this problem, but it should be pointed out that the frequency of small nontuberculous pulmonary lesions simulating tuberculosis (granulomata from various causes, tumors, cysts, vascular anomalies, hematoma, chronic lipoid pneumonia, infarctions, etc.) makes it hazardous to diagnose tuberculosis without bacteriologic proof and to claim success in treatment. A diagnostic thoracotomy is frequently the only method of determining the true nature of such lesions.

Before reviewing the results of excisional surgery for localized tuberculous lesions of the lungs, it seems fitting to comment briefly upon the prognosis of such lesions and the rôle of surgical excision in their treatment at this hospital.

A knowledge of the usual fate of localized tuberculous lesions of the lung is helpful in planning the management and evaluating results of treatment. It must be recognized that such lesions may regress and heal spontaneously. They may respond to proper medical management or remain latent with their fate in doubt for many years. Finally, progression of the disease may occur in spite of proper treatment if the patient's resistance is poor, if therapy prescribed is inadequate to cope with the disease present, or if the patient fails to coöperate.

* From the Symposium on Tuberculosis presented at the Thirty-Fourth Annual Session of the American College of Physicians, Atlantic City, New Jersey, April 15, 1953.

From the Surgical, Medical and Laboratory Services, Fitzsimons Army Hospital, Denver, Colorado.

The prognosis in pulmonary tuberculosis depends upon many factors. Chief of these is the extent of disease when first recognized and the patient's own natural or acquired immunity. Other considerations include social and economic factors, the stress and strain of the patient's work or mode of living, the age and race of the patient, the duration and character of the lung lesion, the persistence and severity of the symptoms, the length of time tubercle bacilli continue to appear in the sputum, the occurrence of complications (tuberculous or nontuberculous), the patient's coöperation in treatment, and proper management.

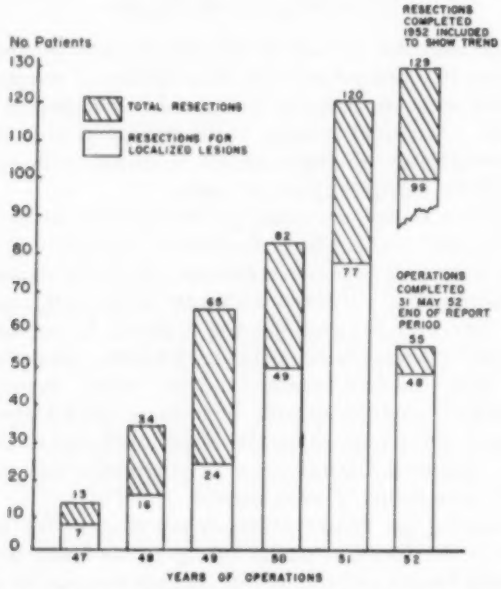

FIG. 1. Surgical removal of tuberculous lesions of the lung, January 1, 1947 to December 31, 1952. (The 221 localized lesions removed through May 31, 1952 are the subject of this report.)

From the foregoing it is evident that many factors over which we have no control affect the prognosis. Nonetheless, the fate of the newly found active lesion of tuberculosis such as is being diagnosed in great numbers by mass chest roentgenographic surveys will depend in a large measure on how the patient accepts his disease and the treatment given. For these reasons it is extremely important to review all factors concerned, inform the patient of the problem and embark on a treatment program (medical or surgical or both) that offers the greatest possibility for success.

It should be recognized that only a small percentage of all tuberculous lesions of the lungs appear to be suitable for resection according to present-

day standards. This is clearly demonstrated by an evaluation of 431 patients with pulmonary tuberculosis treated successfully to the "inactive stage" and discharged in 1952 from Fitzsimons Army Hospital (table 1). It is noted that pulmonary resection was resorted to in 20 per cent of patients, but in fairness it should be pointed out that this number would have been greater if all patients advised to have such treatment had accepted it.

TABLE I

Tuberculosis Patients Discharged from Fitzsimons Army Hospital in 1952 with Inactive Disease
(Min. 30%; MA 58%; FA 12%)

Treatment	No.	%
Medical Treatment	334	77
Rest and drugs	103	23
Drugs and temporary collapse	231	54
Thoracic Surgery	97	23
Thoracoplasty	12	3
Resection-thoracoplasty	61	14
Pulmonary resection	24	6
All resections	85	20
Total	431	100

From experiences such as these it can be concluded that the definitive treatment of tuberculosis is based largely on an estimate of the pulmonary disease present. It should be emphasized that medical treatment plays its greatest rôle in the management of new lesions, particularly those with predominantly reversible disease. Surgical procedures, on the other hand, have their greatest field of usefulness in the eradication of dangerous necrotic foci and cavitary lesions. It is with this group of serious lesions that we will concern ourselves in this review.

EXPERIENCES AT FITZSIMONS ARMY HOSPITAL WITH RESECTION OF LOCALIZED TUBERCULOUS LESIONS

From January 1, 1947, through May 31, 1952, 369 patients received excisional surgery for pulmonary tuberculosis. Of this group 221 patients (60 per cent) manifested by roentgenographic study preoperatively lesions that were classified as localized disease, and follow-up studies of one to five years are available in 98.1 per cent of this series. Most of the patients were young adult white males in good general health except for pulmonary tuberculosis, and all were considered excellent operative risks prior to operation (figure 1).

For the purposes of this report, localized lesions are defined as any tuberculous process, cavitary or noncavitary, involving only one lobe and limited to an area not exceeding the extent of pulmonary parenchyma above the level of the second costochondral junction. This conforms to the area of minimal lesions as defined by National Tuberculosis Association Diagnostic Standards. The excised lesions were classified by the pathologist as tu-

berculoma, caseonodose, caseopneumonic and cavitary. Some difficulty occurred in classifying the lesions into these four groups because the pathologic lesion was frequently of a mixed variety. All lesions revealing cavitation were classed with the cavitary group, even though the process also appeared to fall into other categories. The term "caseopneumonic" was selected to denote the diffuse or poorly circumscribed lesions; "caseonodose," the multiple nodular lesions; and "tuberculoma," the well encapsulated caseous focus. Duration of disease varied from one to 15 years prior to operation, except in the two patients who had caseopneumonic lesions of recent origin. Forty-six per cent of the "tuberculomas" had associated satellite caseonodose lesions.

The bacteriologic studies of the sputum and surgical specimens revealed that 19 per cent of the lesions were not proved to be tuberculous by demonstration of acid-fast bacilli. This group of lesions was shown to be granulomatous disease with caseation and was recorded by the pathologist as consistent with a diagnosis of tuberculosis. Although mycotic and other causes of granulomatous reactions were reasonably well excluded, it is recognized that the diagnosis of tuberculosis has not been completely established. In certain other cases the preoperative diagnosis of tuberculosis was well established by bacteriologic studies of the sputum prior to chemotherapy, but examination of the surgical specimen was negative for acid-fast bacilli. The pathologic findings were consistent with the clinical diagnosis, but the possibility of coexisting mycotic or other infections was always entertained. In one such case the postoperative spread left no doubt as to the accuracy of the clinical diagnosis and served as a reminder that excisional surgery eliminates only the most accessible and localized foci of disease. Lesions of this type were included in the study to point out these diagnostic problems and to illustrate the importance of considering the total picture in evaluating the treatment of localized lesions of the lung believed to be tuberculous.

Except in one instance, the tuberculin test was recorded as positive in all patients proved bacteriologically to have pulmonary tuberculosis. Thus the validity of this test was confirmed in 99.5 per cent.

Chemotherapy was used for short periods before and after operation until 1951. Since this time it has been the practice to use drugs for longer periods to stabilize the lesion prior to operation and then to continue four to six months postoperatively. After it became available in 1949, streptomycin was administered intermittently every three days combined with para-aminosalicylic acid orally daily. Temporary collapse measures were employed in 59 patients (27 per cent) of the series prior to operation.

Excision was accomplished by wedge resection in 68 patients, segmental resection in 38 patients and lobectomy in 115 patients. The various operative procedures are correlated with the pathologic type of disease in table 2. A three to five rib thoracoplasty was performed in 124 patients (56 per cent) to minimize overdistention of the remaining pulmonary parenchyma.

TABLE II

Operative Procedures for the Various Pathologic Types of Localized Pulmonary Tuberculosis
Fitzsimons Army Hospital—January, 1947, through May, 1952

Type of Lesion	No. Pts.	Operations			
		Wedge	Segment	Lobectomy	Associated Thoracoplasty
Tuberculoma	54	34	8	12	20
Caseonodose	96	26	24	46	56
Caseopneumonic	2	0	0	2	2
Cavitary	69	8	6	55	46
Total	221	68	38	115	124

Thoracoplasty was reserved for the lobectomy patients with few exceptions, and the operative procedures were performed in two stages separated by an interval of from three to four weeks.

The postoperative management included bed-rest and hospitalization for approximately one year for most patients with active tuberculosis. Ambulation was not permitted in any case until the disease was at least "inactive" as defined by the 1950 National Tuberculosis Association Diagnostic Standards. Restoration to sedentary employment or full-time school work was not advised until the disease had been inactive six to 12 months, while return to full-time work was not recommended until the disease had been inactive 12 to 18 months.

RESULTS

Early: There were no deaths due to tuberculosis or its complications in the entire series of 221 patients. The only operative death resulted from a blood transfusion reaction (table 3).

Complications in the immediate postoperative period (60 days) were relatively infrequent, and in no instance did the patient fail to recover. The incidence of postoperative tuberculous complications was 2.3 per cent. These included two bronchopleural fistulae, one chest wall sinus, one empyema and one spread of the disease. Nontuberculous complications occurred in 25 instances (11.3 per cent), but recovery was prompt in all (table 3).

Late: Follow-up studies are lacking on four patients (1.9 per cent). Of the remaining 216 patients followed for from one to five years, 207 (93.6 per cent) are alive and well (table 4). Of these, 127 (57.5 per cent) are performing full- or part-time work. Eighty (35.8 per cent) are well but have not yet returned to gainful employment. Seventy-one of these have been operated upon since 1951.

Late complications that occurred during the five year follow-up period were few (table 5). None of these occurred in the tuberculoma group. In five patients reactivation of the pulmonary disease occurred at intervals of

TABLE III

Early Postoperative Deaths and Complications Following 221 Pulmonary Resections for Localized Tuberculous Lesions of the Lung

Factors	Wedge	Seg.	Lobe	Total	%
No. Patients	68	38	115	221	100
Deaths	1*	0	0	1	0.5
TB complications	0	2	3	5	2.2
B. P. fistula†			2	2	
Sinus tract		1		1	
Empyema		1		1	
Spread			1	1	
Non-TB comp.‡	4	2	19	25	11.3
Total	5	4	22	31	14.0

* Transfusion reaction.
† Bronchopleural fistula.
‡ Nontuberculous operative complications (recovery was prompt in all):

Atelectasis	5	Subscapular hematoma	3
Pleural effusion	4	Thrombophlebitis	1
Bronchopneumonia	3	Pulmonary infarction	1
Pneumothorax	3	Fractured ribs	1
Postoperative bleeding	3	Anesthesia reaction	1

four, five, seven, nine and 11 months postoperatively. The reactivation of previously unrecognized foci of infection occurred on the side of the resection in three cases and in the contralateral lung in one case. Bacteriologic relapse occurred in one instance without evidence of endobronchial disease or new pulmonary lesions. Glandular tuberculosis occurred in two patients. Both were proved by biopsy and bacteriologic examination. One patient developed axillary adenitis four years after pulmonary resection, while the other case was a reactivation of previously existing cervical adenitis four years after operation. Follow-up revealed two late nontuberculous deaths,

TABLE IV

Late Complications Correlated with Operative Procedure and Pathologic Specimen
216 Patients Followed 1 to 5 Years Postoperatively

Tuberculous Lesions		Complications Occurring with Various Operative Procedures			
Type	No.	Wedge (68)	Segment (38)	Lobectomy (115)	Total
Tuberculoma	54	0	0	0	0
Caseonodose	96	1 Reactivation*	1 Reactivation* 1 Extrapul.†	0	3
Caseopneumonic	2	0	0	0	0
Cavitary	69	0	0	3 Reactivation* 1 Extrapul.†	4
Total	221	1	2	4	7 (3.2%)

* Pulmonary reactivation.
† Extrapulmonary complications were glandular tuberculosis in both instances.

TABLE V

Follow-Up Study of 221 Patients Receiving Pulmonary Resection for Localized Tuberculous Lesions of the Lung During the Period January, 1947, to May, 1952

Factors	Status of Patients by Year of Resection			Total	%
	47–48	49–50	51–52		
No. Patients	23	73	125	221	100.0
Deaths	1	2	0	3	1.3
TB	0	0	0	0	0.0
Non-TB	1	2	0	3	1.3
Alive and well	21	69	117	207	93.6
Working	21	60	46	127	57.5
Full-time	17	42	32	91	41.1
Part-time	4	18	14	36	16.3
Not working	0	9	71	80	36.1
Active TB	1	2	4	7	3.2
Pulmonary	0	1	4	5	2.2
Extrapulmonary	1	1	0	2	1.0
No follow-up	0	0	4	4	1.9

one following trauma, the other attributed to acute alcoholism. There were no late deaths due to tuberculosis.

DISCUSSION

Follow-up evaluation of patients with localized tuberculous lesions of the lung removed by surgical excision at Fitzsimons Army Hospital during the period January, 1947, to May, 1952, revealed a very low morbidity and mortality rate and indicated that the vast majority of patients so treated can be restored to good health and normal productivity (tables 3, 4 and 5). It is recognized that the follow-up period is too short for final evaluation.

Control studies of a comparable group of cases treated by medical measures (rest, drugs and temporary collapse) at Fitzsimons Army Hospital during the period of this study are not available for comparison. This would be desirable, but there are practical reasons why such a study was not possible. Many of the cases presented in this series were those which failed to respond to medical measures, others were promptly classified as old active fibrocaseous disease, and many others were diagnostic problems. Noncavitary minimal lesions proved to be tuberculous represent the only group of lesions discussed in this report potentially suitable for medical treatment. Minimal lesions were seldom treated by chemotherapy at this hospital until 1951, and it was not until 1952 that such therapy was prolonged to the stage of arrested or inactive disease. This new approach to drug therapy may reduce the need for surgical excision in the smaller necrotic lesions, but many years of clinical investigation will be required to

answer this question. It should be pointed out also that the relapse rate in patients with minimal pulmonary tuberculosis treated by rest alone prior to the introduction of streptomycin was very high.[1, 2, 3] While this has been reduced by the use of specific drugs, it still remains a serious problem to be solved. Many factors, not at once apparent in studies of this type, add to the difficulty of advising the best approach to therapy at this time.

Summary and Conclusions

1. A preliminary report on results of pulmonary resection of localized necrotic tuberculous lesions of the lung has been presented on 221 patients followed one to five years postoperatively. This review is restricted to lesions of the lung involving only one lobe and limited to an area not exceeding the extent of a minimal lesion as defined by National Tuberculosis Association Standards. Sixty-nine of the lesions were cavitary, two were diffuse caseopneumonic, 96 were caseonodose and 54 were tuberculoma. The operative procedures used in this series were 68 wedge resections, 38 segmental resections and 115 lobectomies.

2. Background factors that must be considered in the evaluation of the surgical treatment of pulmonary tuberculosis have been reviewed and its place in definitive treatment has been discussed.

3. One to five year follow-up evaluation of 98.1 per cent of these patients revealed that results from excision of necrotic tuberculous pulmonary lesions have been most gratifying. Operative mortality was 0.5 per cent. The incidence of postoperative tuberculous complications was 3.2 per cent, late pulmonary reactivation, 2.2 per cent; and late extrapulmonary disease (glandular), 0.9 per cent. Ninety-three per cent of the patients were well and should be capable of resuming employment soon, while 75 per cent of those operated upon prior to 1952 are working.

4. It should be emphasized that this is a retrospective study dating back to 1947, and that during this period much progress has been made in the treatment of pulmonary tuberculosis. It is anticipated that new concepts in management will be introduced in the future, and it is hoped that experiences such as we have reported will serve as a guide to improve further the treatment of this serious disease.

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LATE RESULTS OF TREATMENT OF THE SOLITARY DENSE TUBERCULOUS PULMONARY FOCUS (TUBERCULOMA) WITHOUT RESECTION OR CHEMOTHERAPY *

By ROGER S. MITCHELL, M.D., F.A.C.P., *Trudeau, N. Y.*

INTRODUCTION

THE solitary dense pulmonary focus is now frequently treated by pulmonary resection. There are two reasons given for advising this type of treatment: first, the lesion may be malignant and amenable to surgical extirpation; and second, the results with nonsurgical treatment of so-called tuberculoma are reputed to be unfavorable.

Abeles and Ehrlich, among many others, have stressed the uncertainty of diagnosis in these dense circumscribed lesions picked up on surveys. They were able to follow 44 cases which had been found on routine survey in Massachusetts. Twenty-seven per cent were proved to be malignant by means of pathologic examination after thoracotomy, the finding of malignant cells in the sputum, or the subsequent behavior of the lesion; and only 40 per cent were proved to be tuberculous.[1] Culver et al. treated 23 such cases with resection because of fear not only of malignancy but also of potential relapse if tuberculous, and all of the nine thoracic surgeons who discussed this paper in 1950 expressed general agreement with this point of view.[2]

On the other hand, the published *results* of the non-resectional treatment of these lesions in tuberculosis hospitals have not been too unfavorable. Moyes observed 33 Brompton Hospital patients for from three to 15 years after rest, temporary collapse or no treatment. In 1951, 30 were well and three were ill with tuberculosis, none had died, but roentgenographic instability of the disease had been noted at some time in 52 per cent.[3] Eriksen followed 40 such patients in 1949 for from two to 11 years after conservative management, of whom 38 were well at the end of the observation period.[4]

Birkelo and Kasper (1937) observed 60 patients for from six months to six years after treatment with rest, with or without pneumothorax or phrenic nerve interruption, of whom only five had extension of disease during this variable follow-up period. They felt that a tuberculoma originating from conglomeration of previous exudative disease was more prone to reactivation than one which was circumscribed from the outset or which appeared at the time of primary infection.[5] Pugh and Jones agreed with

* From the Symposium on Tuberculosis presented at the Thirty-Fourth Annual Session of the American College of Physicians, Atlantic City, New Jersey, April 15, 1953.

From Trudeau Sanatorium, Trudeau, N. Y.

This study was made possible by a grant from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association.

this point of view; they observed no deaths, but there were seven reactivations in 28 patients followed for from six months to three years in 1952.[6]

There is fundamental disagreement between these two groups of papers on the question of malignancy. The average age of the patients in the four series reported from tuberculosis centers with no malignancy was below 30, whereas in the two survey groups with a considerable proportion of malignancy, the average age was well above 40. It must be concluded that the patients observed in tuberculosis centers had been well screened for malignancy before admission to the sanatorium.

Two reports were found on late results of inspissated tuberculous cavities, which may or may not be comparable to solitary dense foci. Study and Morgenstern followed 24 cases with inspissated cavity for from six months to seven and one-half years. All but one had received collapse (phrenic nerve interruption, pneumothorax or thoracoplasty), and all were continuing to do well at the end of the observation period.[7] Bernou and Tricoire followed 128 inspissated cavities for from one to 27 years: reappearance of cavity occurred in 26 per cent of 63 treated without collapse, in 32 per cent of 53 treated with pneumothorax, in three of six treated with phrenic nerve interruption, and in three of six treated with thoracoplasty.[8] Houghton regarded the inspissated cavity as a "time bomb" but gave no supporting data.[9]

Early results of the resection of tuberculomas, even without covering chemotherapy, have been quite favorable in various clinics, but the determination of *late* results following operation must necessarily await the passage of more time. Late results with these lesions when treated by so-called conservative methods—bed-rest alone, bed-rest plus phreniclasia, pneumothorax or pneumoperitoneum—are available and provide a background for the assessment of the results not only of surgical extirpation but also of prolonged chemotherapy.

Materials and Methods

The clinical records of all patients admitted to Trudeau Sanatorium between January 1, 1930, and December 31, 1949, were searched for instances of solitary dense pulmonary foci. Many cases were found among patients classified as "Minimal" on admission. A few had solitary dense foci after disappearance of cavity with or without pneumothorax or phrenic nerve interruption.

Only 40 patients were found whose disease consisted *principally* of one or more solitary dense foci at some time prior to discharge; 33 had single lesions, six had two foci, and one had three. The case records and roentgenograms were reviewed, the patients were followed by yearly and special questionnaires, and in 34 a review of roentgenograms to 1950–52 was possible. Contact was maintained to 1952–53 in 37 cases, and three others had been well since discharge, when they were lost after eight, 17 and 18

years of follow-up, respectively. The duration of follow-up ranged from four to 22 years.

The age range was 19 to 50, with a mean of 28 years. There were 27 females and 13 males. About 55 per cent of all admissions during these 20 years were females. Pugh and Jones found this lesion more common in females.[6] All were classified as "minimal" in extent at the time of discharge, but cavity had previously been observed within the dense focus in 29 of the 40. Seven had been treated with pneumothorax, four with phrenic nerve interruption, and one with pneumoperitoneum. One received 12 gm. PAS daily for three months and another 1 gm. streptomycin intramuscularly daily for 60 days, but no other patients had received specific chemotherapy. All received modified bed-rest. (Modified bed-rest is defined as 20 to 21 hours per day reclining in bed or on a chaise-lounge with meals eaten in an adjoining room, full bathroom privileges, and occasional permission to travel to other buildings for necessary examinations.) These 40 patients were given from 1 to 25 consecutive months (mean, 7 months) of modified bed-rest. They spent from two to 32 months (mean, 10 months) on sanatorium treatment.

Progression of disease is defined as any known development or reappearance of cavity within the dense focus or appearance of new shadows on the chest roentgenogram. There was no instance of development of positive sputum without other manifestations of relapse or of extrapulmonary tuberculosis.

The dense foci were located as follows:

Apex	7
Infraclavicular region	22
Midlung	7
Base	3
Both lungs	1
Total	40

Twenty-nine of the 40 patients had symptoms suggestive of pulmonary tuberculosis. Diagnosis was confirmed by sputum found positive for acid-fast bacilli by 50-hour concentrated smear, or for *Mycobacterium tuberculosis* by culture of sputum or gastric washing in 65 per cent. The tuberculin test was positive in all patients with negative sputum findings.

Results

One case with a 3 cm. nodule below the level of the right hemidiaphragm proved to be a benign fibroleiomyoma on pathologic examination following resection. No tumors, malignant or benign, have been proved in the other 39 cases.

The cumulative rate of progression in the 39 cases was 26.1 per cent projected over 22 years by the Life Table Method (figure 1). Not only is this cumulative relapse rate somewhat lower, but the curve rises more

slowly than has been observed in active minimal tuberculosis.[10] Two of the nine patients with progression became quite ill and were disabled for many years before attainment of relatively good health. Six had one progression followed after treatment by uninterrupted good health, and

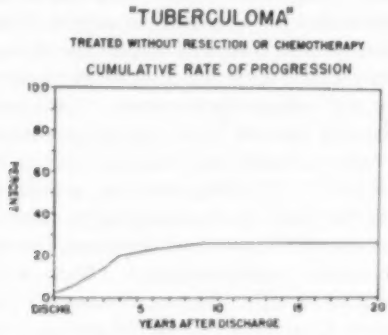

FIG. 1. Cumulative rate of progression in 39 cases of solitary dense tuberculous pulmonary focus (Life Table Method).

in one, there were two separate progressions (or relapses). The treatment for the relapses in these nine cases was thoracoplasty in two, streptomycin or streptomycin-PAS in four, and bed-rest alone in the balance.

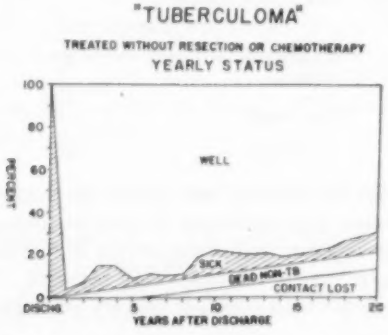

FIG. 2. Behavior of 39 cases of solitary dense tuberculous pulmonary focus during 20 years following discharge after treatment without surgery or chemotherapy. Proportions in each year are based upon number of patients with whom contact was still maintained.

The long-range clinical behavior of tuberculosis in the 39 patients with these lesions is shown in figure 2. Withdrawals caused by nontuberculous deaths and loss of contact are shown in the lower portion of the figure.

The 1952 status of the 39 patients is shown in table 1.

The possible relationship of various factors to the chance of progression was studied. The presence of visible cavity or a positive sputum at some

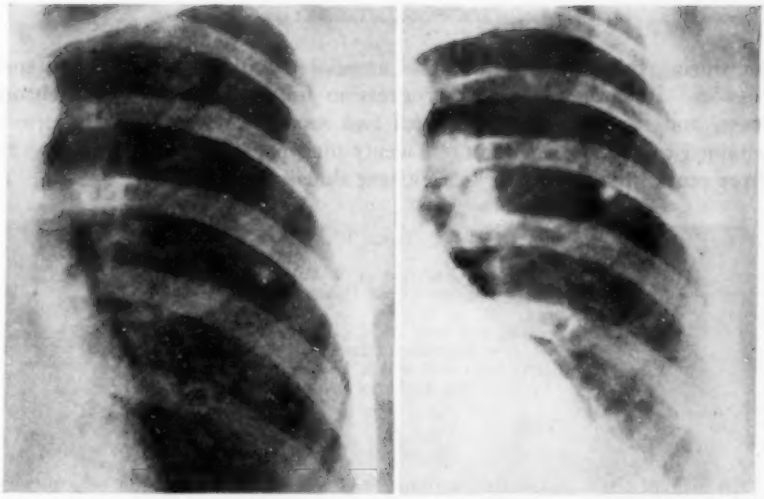

FIG. 3. *Case 1.* M. D., 32, nurse; mild cough and expectoration and routine film led to admission; (left) admission film 1933; 2 cm. nodule containing .5 cm. cavity in first left anterior interspace; concentrated sputum smear, Gaffky ii; 26 months at sanatorium; (right) 1951 film; well for 16 years.

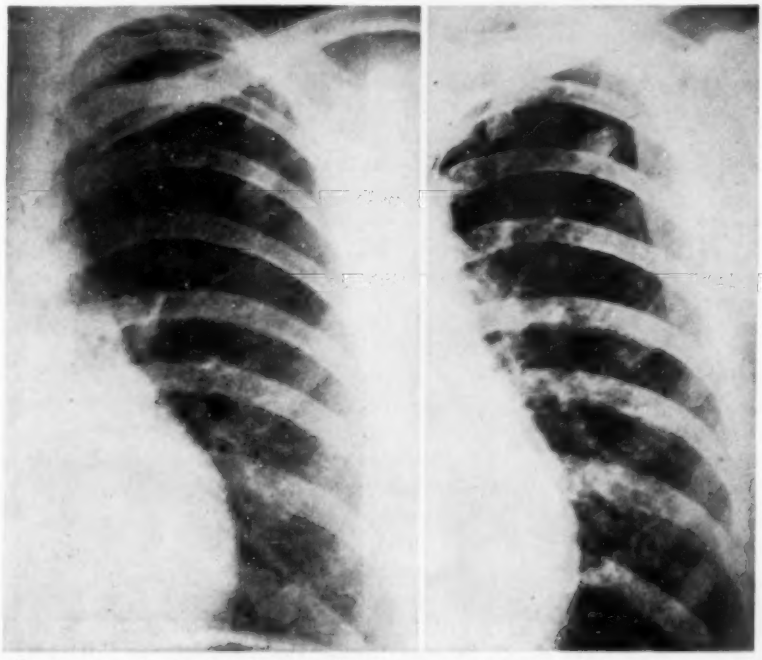

FIG. 4. *Case 2.* R. C., 26, housewife; hemoptysis led to admission; 1.5 cm. nodule over second left anterior rib; (left) admission film, 1930; no cavity seen; 4 concentrated sputum smears negative; 2 months at sanatorium; (right) 1951 film; well for 21 years.

time during initial observation was associated with a higher rate of progression. In both cases with progression followed by prolonged chronic illness, and in the one patient with two separate progressions, the focus contained cavity at the outset. Twenty-nine per cent of the cavitary and 17 per cent of the noncavitary cases have shown progressions.

TABLE 1

1952 Condition of 38 Patients with Solitary Dense Pulmonary Foci

Working and well	34
Dead, nontuberculous causes	2
Contact lost; still well 8, 17 and 18 years after discharge	3
Total	39

In nine of the cases with the dense focus in the midlung or base, only one progression occurred. Those receiving collapse had a higher relapse rate than those not so treated. This is probably explained by the presence of

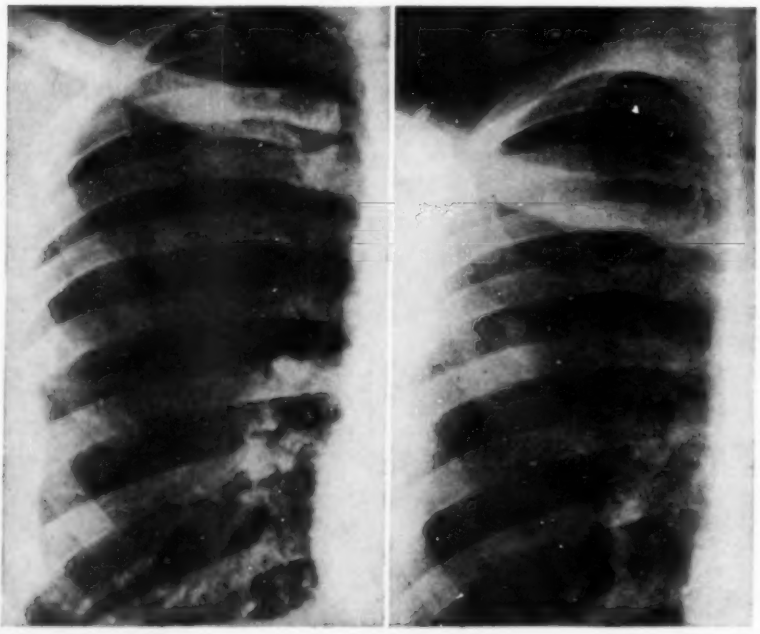

FIG. 5. *Case 3.* R. K., 27, physician; routine film, no symptoms; (left) admission film, 1935; 2.5 cm. nodule in second left anterior interspace; no cavity seen; concentrated sputum smear, Gaffky ii; (right) after 4 months at sanatorium; well until cavity appeared in dense focus in 1944, 9 years later; well to 1953 after 1 year of additional treatment.

more extensive disease and a greater incidence of cavity in the collapse-treated cases.

Two examples which did not have reactivation are shown in figures 3 and 4.

Figures 5 and 6 show two cases which did have reactivation.

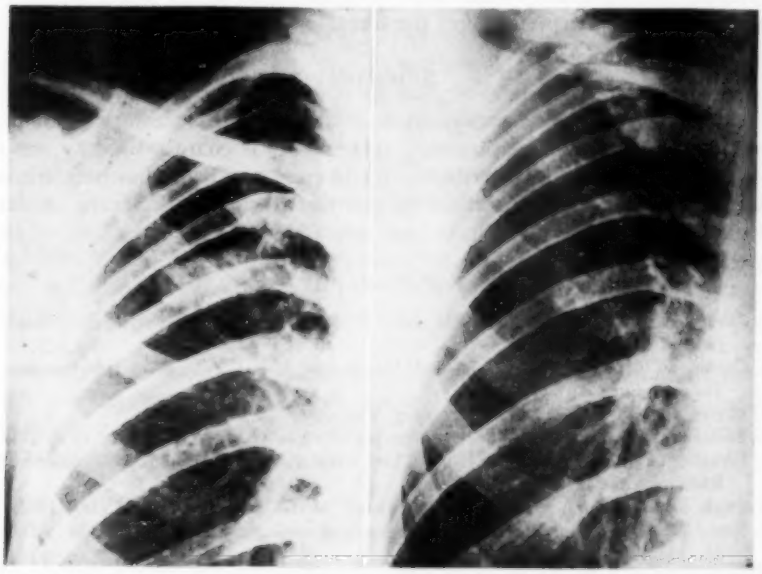

FIG. 6. *Case 4.* S. F., 27, physician; loss of weight and strength; (left) admission film, 1940; oblong 2×4 cm. nodule over second right anterior rib; no cavity seen; all sputum negative by concentrated smear and culture and gastric washing cultures; (right) 1951 film; patient had mild local spread 6 months after completing 13 months of sanatorium treatment; responded promptly to rest treatment and has been well since to 1953.

COMMENT

The absence of malignancy from this group was striking. Several cases with pulmonary malignant lesions were misdirected to Trudeau Sanatorium during the 20-year observation period, but none was found which took the form of a solitary dense circumscribed focus. This may represent a valid observation concerning the etiology of this type of lesion in the 18 to 50 year age group, or it may reflect very successful selection before admission. In any event, the reports from other tuberculosis sanatoriums made the same observation.[2, 4, 5, 6]

The small size of this and other samples of similar material suggests that these lesions may occur less frequently than commonly supposed. End results were quite comparable to those reported from other tuberculosis centers,[3, 4] except that the rate of progression of tuberculosis was higher in one other series.[3]

It would appear logical to treat these lesions by some method other than simple rest with or without temporary collapse in order to reduce the moderate risk of relapse. Resection or prolonged combined chemotherapy, or both, all appear promising on the basis of early results. If surgical measures are not to be used in these cases, however, all reasonable doubt about the possibility of malignancy must have been removed by careful examination and experienced interpretation of the films.

Summary

After prolonged observation, there is about one chance in four of progression of disease when pulmonary tuberculosis is characterized by one or more solitary dense circumscribed foci (tuberculomas) and has been treated without chemotherapy, resection or permanent collapse. Severe or fatal progressions of such lesions have been rare.

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CHOLANGIOGRAPHY *

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WHEN most indicated, oral cholecystography is least reliable. It is most reliable when the biliary system is normal, and least reliable in the presence of disease. Visualization usually fails when this examination is most indicated—in the differential diagnosis of intrahepatic and extrahepatic obstruction. The cystic and common ducts are rarely visualized sufficiently for diagnosis, even when opacification of the gall-bladder is optimal. Another means of opacifying the gall-bladder and ducts which does not entail laparotomy is desirable.

Added experience with cholangiography performed during peritoneoscopy reaffirms the value of this procedure in disease of the biliary system. There is little written evidence that this procedure is being used widely, although Lee [1] recommended it in 1942 and Hodges [2] in 1944. Royer and co-workers [3, 4] have stressed the technical simplicity and value of peritoneoscopic cholangiography. We [5] emphasized in an earlier report the usefulness of the method in diseases of the biliary tract which defied other means of diagnosis.

TECHNIC

The technic is discussed in the earlier report. Preparation of the patient is the same as for peritoneoscopy. After visualizing the gall-bladder peritoneoscopically, a 5 inch 20 gauge needle is inserted through the abdominal wall overlying the gall-bladder. It is guided, under direct vision, to the area of the fundus and is inserted with a quick thrust through the gall-bladder wall. A free flow of bile is then established and 5 to 50 c.c. of bile are aspirated. Ten to 15 c.c. of 35 per cent iodopyracet are injected and roentgenograms obtained.

We have made some slight changes in the technic. In approximately 20 per cent of patients the gall-bladder is deeply situated underneath the anterior edge of the right lobe of the liver and is covered by omentum and bowel. By a sweeping motion with the needle it is possible to displace the other abdominal contents and visualize the gall-bladder. Usually those patients in whom the gall-bladder is the most difficult to find are those in whom the procedure is most indicated, since the gall-bladder is usually small

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and contracted in association with chronic inflammation and intraductal stone.

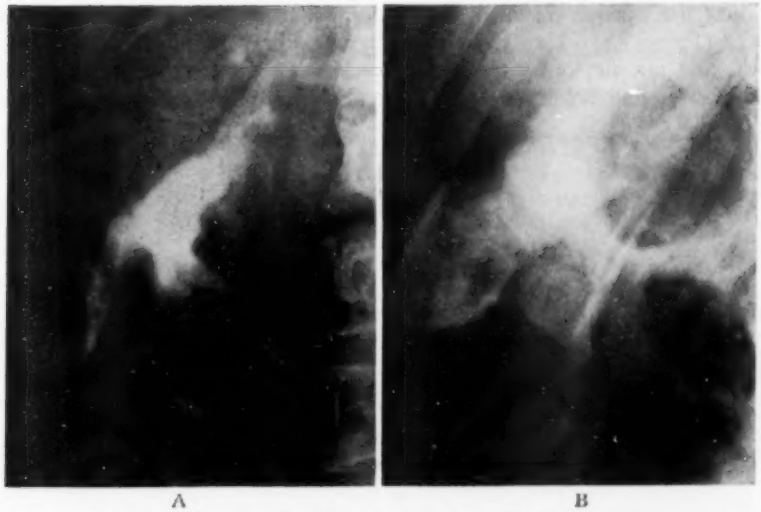
We no longer use air for contrast since even large amounts will not displace the bile within the ducts and produce an interpretable shadow of negative density on the roentgenogram. Heretofore, we used 20 to 50 c.c. of concentrated solution of iodopyracet after aspirating rather large quantities of bile (30 to 50 c.c.). We have found that the roentgenograms are equally good after aspirating only a small quantity of bile and injecting 10 to 15 c.c. of 35 per cent iodopyracet. After completion of the injection, nitroglycerin (0.4 mg.) is administered sublingually. We no longer have a definite schedule for obtaining the roentgenograms but obtain one scout

FIG. 1. Normal gall-bladder with filling of the cystic and common ducts. Dye is beginning to enter duodenum.

film to determine the optimal position to visualize the ducts and discontinue exposures after obtaining adequate roentgenograms of the dye-filled gall-bladder, cystic and common ducts (figure 1).

MATERIAL AND RESULTS

Fifty-five direct cholangiographic examinations have been performed during 787 peritoneoscopic examinations. Clinically it was not possible to differentiate between hepatocellular damage and extrahepatic biliary obstruction. Liver function studies, if abnormal, were equivocal, and the gall-bladder was not visualized adequately after oral cholecystography with a

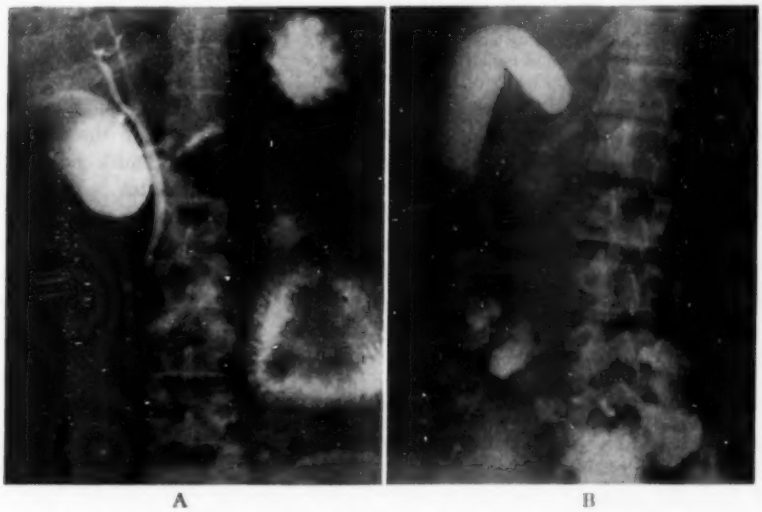


A B

FIG. 2. *A*. Intramural and extravasated dye. *B*. Intramural dye.

double dose of dye. Visualization of the cystic and common duct was felt to be advisable in each case prior to institution of a therapeutic regimen.

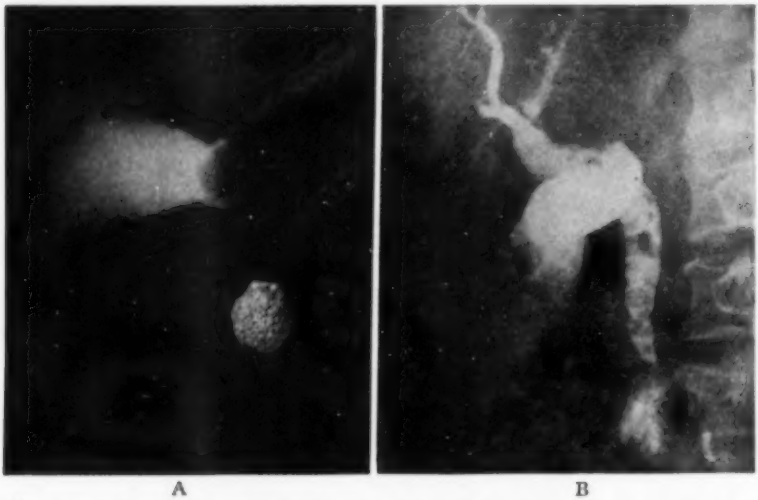
Eighteen of the patients had normal gall-bladders and ducts and were found grossly and histologically to have cirrhosis of the liver. Ten had



A B

FIG. 3. *A*. Gall-bladder with filling of the cystic and hepatic ducts. Retrograde gastric filling and small intestinal filling are evident. *B*. Filling of gall-bladder and colon in a case of cholecystocolic fistula.

solitary non-opaque calculi or multiple small stones in the gall-bladder and ducts (figure 4). Two showed retrograde filling of the stomach (figure 3A), and one demonstrated a communication between the fundus of the gall-bladder and colon (figure 3B). One had obstruction and dilatation



A B

FIG. 4. *A*. Large solitary stone impacted in opening of cystic duct. The stone which was removed is superimposed. *B*. Multiple shadows of negative density with marked dilatation of cystic, hepatic and common ducts. Stones were evident in the gall-bladder, cystic, common, common hepatic and both hepatic ducts. Thirty-five calculi were removed at the time of cholecystectomy and choledochostomy. This patient was thought clinically to have carcinoma of the gall-bladder.

of all ducts in association with carcinoma of the head of the pancreas. The remaining 24 examinations were performed upon patients with suspected biliary tract disease who proved to be normal, patients with metastatic carcinoma to liver, and a variety of other pathologic states. Two with intramural dye and three in whom air was used for contrast are included.

Of the 10 patients with cholelithiasis, eight had nonvisualization with a double oral dose of dye, one had a normal cholecystogram, and one was a psychotic patient in whom it was impossible to obtain a cholecystogram. Retrograde filling of the hepatic ducts was often seen in the presence of normal ducts.

REACTIONS

The use of lesser amounts of 35 per cent iodopyracet solution has decreased considerably the abdominal discomfort experienced by the patient. In the few patients who apparently retain dye for considerable periods, administration of sublingual nitroglycerin alleviated the spasm and permitted visualization of the ducts. We have had no further difficulty with

injecting the dye into the gall-bladder wall or into the peritoneal cavity (figure 2). These eventualities are simply surmounted by assuring a free flow of bile prior to injecting the contrast medium.

Comments

The jaundiced patient can be one of the most perplexing and exasperating patients with whom the internist has to deal. This type of patient can be an urgent surgical therapeutic problem, or he can have a disease which contraindicates general anesthesia and major surgical procedures. Hepatitis and cirrhosis may have an explosive colicky onset, and "silent" stones in the biliary ducts are not unusual. Occlusion of the common duct by carcinoma of the head of the pancreas, or ductal carcinoma, is often not painless as classically described. The facts stated above, although not necessarily applying to a majority of jaundiced patients, apply to a sufficient percentage to make early accurate diagnosis mandatory.

In 18 patients with cirrhosis in this series and in 15 patients reported by Jarvinen and Paltia,[6] the gall-bladder failed to visualize by the oral route.

The gall-bladder is visualized in nearly all routine peritoneoscopic examinations. Vision is precluded only by the presence of rather massive adhesions in the right upper quadrant, usually the result of prior surgical procedures in this area. The information obtained is equal to that of cholangiography performed at the time of laparotomy.

Summary

Fifty-five cholangiographic examinations have been performed during 787 peritoneoscopic examinations.

Visualization of the gall-bladder, cystic and common ducts has been the only means of differentiating intrahepatic and extrahepatic obstruction when other means of cholangiography failed.

The procedure is simple and often spares the patient the rigors of laparotomy.

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THE MANAGEMENT OF BILIARY TRACT DISORDERS IN PATIENTS WITH HEART DISEASE *

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The purpose of this report is to aid in the understanding and management of the cardiac patient with a disorder of the biliary tract. Individuals in this important group may be a joint problem for both internist and surgeon; those coming to operation often present an additional problem in anesthesiology. In an effort to facilitate the care of these patients, we are presenting (a) a discussion of the underlying physiologic disturbances; (b) the results of operation in eight selected cases, and (c) a brief discussion of basic principles of medical, surgical and anesthetic management.

Acute conditions, quite frequently met within this group, include (1) a myocardial infarction diagnosed as cholelithiasis or acute cholecystitis, with a resultant possibly fatal operation; (2) a biliary colic in a known cardiac patient, diagnosed as an anginal attack or a coronary thrombosis, and (3) an acute cholecystitis diagnosed as a coronary thrombosis, in which case the immediate use of anticoagulants may further increase the hazard of a necessary operation. In *chronic* conditions irreparable progressive damage to the biliary tract may result from recurrent biliary attacks which have been diagnosed as angina pectoris.

Clinically, each patient may be considered to present certain practical questions. Among those often requiring prompt decision and action are: (a) Are the symptoms due to the heart, the gall-bladder, or both? (b) Are symptoms apparently of cardiac origin caused or aggravated by a disorder of the biliary tract? (c) Is an operation on the biliary tract indicated? (d) Can the patient withstand the operation? (e) What results can be expected following an operation? Experience clearly indicates an individualized course of management. We hope to assist others in answering these pertinent questions by a review of known facts and of our own experience.

The problem in differential diagnosis and management is presented more frequently in the older age group, especially in women. That both cardiac disease and biliary tract disorders are present in a large proportion of persons who die after the age of 40 years has been demonstrated by statistical studies of autopsy findings in large groups of individuals.[1, 2, 3] Both clinical and autopsy evidence indicates that many of these patients

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probably died prematurely. The fault at times lies in lack of early recognition of either one or both of the pathologic conditions.

This discussion is concerned primarily with the clinical aspects of related biliary tract and cardiac disorders. Inasmuch as pain is almost invariably the predominating and at times the only complaint, we are particularly interested in the etiology, mechanism and management of this symptom.

There is general agreement that surgery is indicated for right upper quadrant pain characteristic of biliary colic, especially when there is demonstrable evidence of biliary tract pathology such as cholelithiasis. It is not generally realized, however, that in half of these patients coming to operation the pain is in the epigastrium, at times with radiation to the precordial area. Since epigastric and precordial pain also may be of cardiac origin,[5] the importance of accurate differential diagnosis at once becomes apparent.

Physiologic Considerations

The nervous mechanism whereby stimuli originating in the gastrointestinal or biliary tracts may result in anginal-like pain [5] has been reviewed by Cady, Shallenberger and Koloski.[6] According to these authors the sensory nerve endings of the heart and coronary arteries are innervated by the motor-sensory fibers of the vagus and the sympathetic fibers from the four upper thoracic segments of the spinal cord. The nerve supply of the gall-bladder is derived from the right vagus and the splanchnic nerves through the celiac plexuses; the branches of the splanchnic nerves may extend as high as the first or second thoracic sympathetic ganglia. Whereas cardiac pain usually involves the upper thoracic segments of the left side, with either cardiac or biliary tract pain there may be involvement of the ganglia of the right side, with resultant epigastric pain. Gall-bladder disease may produce anginal-like pain by referral of stimuli to the upper thoracic segments by way of fibers of the great splanchnic nerve.

Conceding the above relationships of the autonomic nervous system, the major problem involved is whether in any given case the anginal-like pain results from: (1) changes in the biliary tract without actual participation of the heart, or (2) reflex stimulation of the coronary arteries which occurs as the result of stimuli originating in the gastrointestinal or biliary tracts.

Clinically and experimentally, overdistention of the gastrointestinal or biliary tracts has been found to have the following effects upon the heart: (1) the production of anginal pain [5, 7-9]; (2) disturbances in cardiac rhythm and output, including shock, heart block and cardiac standstill [7, 10-13]; (3) changes in the R-T segments and T waves of the electrocardiogram.[4-6, 7, 8, 14, 15] The above changes, whether produced clinically or experimentally, have been prevented in most of the reported cases by vagotomy or the use of atropine.

Blumgart [17] has shown that anginal pain and the cardiac abnormalities described may result from cardiac ischemia, whether produced by pathologic, functional or experimental means. This author stated that in 90 per cent of patients having these findings the primary cause is atherosclerosis of the coronary arteries. He also found that reflex coronary spasm played an important part, both in the production of pain and in infarction as a result of acute coronary occlusion. These facts suggest that both the pain and the cardiac abnormalities may be the result of pathologic cardiac conditions aggravated by stimuli originating in the biliary tract.

Animal Experimental Studies: In the experimental animal, both overdistention of various parts of the biliary tract and prolonged vagus stimulation of the coronary arteries have reduced coronary blood flow and produced coronary thrombosis and degenerative changes of the cardiac muscle, with resultant electrocardiographic changes.[9, 12, 16] In animals with experimentally-produced lesions of the coronary arteries, Hodge and Messer [10] found changes in the R-S-T segments comparable to those produced by prolonged overdistention of the biliary tract. Overdistention of the biliary tract was found to produce significant changes in the cardiac rate, rhythm and output only in the presence of induced cardiac pathology.[8, 18] Chronic overdistention of the biliary tract was found by Schrager and Ivy [18] to occur one week after a partial common duct obstruction.

Gilbert [16] concluded that in general the abnormal symptoms, the disorders in cardiac function and the electrocardiographic changes described above occurred from vagal stimulation of the heart only when extensive cardiac damage had previously been induced. In those animals having a lesser degree of cardiac damage, the abnormal findings could be corrected by the removal of the vagal stimuli.

Human Experimental Studies: In a series of patients with chronic arteriosclerotic cardiovascular disease, Morrison and Swalm [7] produced typical attacks of angina pectoris, cardiac irregularities, cardiac standstill and changes in the R-T segments of the electrocardiogram by the pneumatic distention of the stomach and various levels of the esophagus. The pain was relieved and the changes described returned to normal after release of the distention pressure. The preliminary use of atropine served as a preventive. The pain and abnormalities of the heart did not occur in the same patients when the experiments were repeated following a period of dietary and medical management directed toward the relief of the irritability of the gastrointestinal tract. Morrison and Swalm attributed these findings to a reflex arc between the upper digestive tract and the heart, in which cardiac ischemia resulted from coronary vasoconstriction. The precipitating factor was apparently the trigger mechanism of an irritable and sensitive gastrointestinal tract. By distention of the gall-bladder and bile ducts, Hodge and Messer [10] also produced pain and respiratory distress in 26 human subjects. The electrocardiograms showed changes in rate and rhythm, with T wave changes only in those patients with coronary disease.

That typical attacks of anginal pain also can be produced by experimental distention of the human common bile duct has been demonstrated by Ravdin,[8] who operated upon two women patients, each 48 years of age, with histories of repeated anginal attacks not relieved by medical therapy. In one patient there was at operation a thick, kinked common duct plastered with adhesions, the duct containing "mud" but no stones. In the other there were stones in the gall-bladder but none in the common duct. The anginal attacks in both were relieved following operation, but in each case the pain could be reproduced by distention of the common bile duct by the introduction through a "T" tube of water under 400 to 500 mm. pressure. In each case the attacks were stopped by the release of pressure or by the inhalation of amyl nitrite.

Ravdin [8] concluded from these studies that the anginal attacks occurred in cases with preëxisting heart disease because of a reflex constriction of the coronary arteries. The stimuli causing this constriction, he believed, could be stones, obstructive or inflammatory lesions of the biliary tract, or experimental distention of the common bile duct. The surgical relief of the angina in these patients apparently was possible because the cardiac lesions per se had not progressed to the point of causing cardiac ischemia.

Clinical Observations

Gilbert [16] has concluded that in the human being chronic overdistention of the biliary tract can produce pain and cardiac abnormalities comparable to those found in the experimental animal with cardiac damage and manipulation of the biliary tract. Similar abnormalities in cardiac function have been noted following overdistention of the esophagus, secondary to cardiospasm or other forms of esophageal obstruction.[7, 16, 20] White [16a] has stated that functional disorders of the heart also may occur as the result of a hiatus hernia or overdistention of the stomach or colon.

Among others, White [16a] and Friedberg [19] have stressed the frequency with which gall-bladder disease and cardiac disorders have been found clinically in the same patient. Furthermore, Clarke [12] has attributed cardiographic changes in the human being with gall-bladder disease to reflex constriction of the coronary arteries, caused by stimuli originating from inflammation or ulceration of the gall-bladder wall.

Results of Surgery

Generally speaking, the clinical results of cholecystectomy in patients with heart disease have been variable. Wolferth [21] stated that "most patients with angina, auricular fibrillation, heart block, extrasystoles or cardiac failure are not cured by cholecystectomy." It is to be noted that these conditions are evidence of advanced coronary disease. Willius and Fitzpatrick,[26] in a review of 229 cardiac patients having had operations

upon the biliary tract, found that 54 per cent were improved. These authors concluded that the diseased gall-bladder apparently exerted a detrimental effect upon the progression of the cardiovascular disease. They considered that in the cardiac patient removal of the diseased gall-bladder was indicated, provided there was a careful selection of cases and the most expert of surgical and anesthetic services were available.

There have been many other reports of patients in whom cholecystectomy has been followed by the relief of pain attributed to the heart and the restoration to normal of cardiac irregularities and abnormalities of the electrocardiogram.[3, 8, 19, 23-26]

As an example of the results reported by various investigators, we cite those of Fitz-Hugh and Wolferth,[22] who found that in certain cases cholecystectomy was followed by (1) the abolition of abnormal cardiac mechanisms; (2) restoration of compensation; (3) the relief of anginal pain, and (4) the disappearance of abnormalities in the electrocardiogram.

Personal Experiences

As with others, our own experiences with cholecystectomy in cardiac patients have been variable. Following are illustrative cases of biliary tract and myocardial disease proved at operation, classified as follows:

1. Cholecystectomy successful in relieving digestive and cardiac symptoms, with postoperative evidence of improvement in the biliary tract and in the cardiac symptoms and findings.
2. Cholecystectomy successful in the relief of digestive but not cardiac abnormalities.
3. Cholecystectomy which resulted in no improvement, or in the death of the patient.

Case Reports

GROUP I

Case 1. An example of cholecystectomy relieving both biliary tract and cardiac symptoms:

A 54 year old man was seen in 1934 with a history of attacks of "acute indigestion" for eight years. There had been five attacks of epigastric pain, weakness, excessive perspiration, nausea and difficulty in breathing. The last attack of severe epigastric pain and vomiting had occurred four months before admission. All attacks tended to occur after exertion or dietary indiscretions.

At the time of the last attack the patient was found to be in shock, with cardiographic findings suggestive but not diagnostic of coronary occlusion. The diagnosis of coronary artery disease was made at that time. Subsequently cholecystography revealed a large solitary calculus in the gall-bladder. Cholecystectomy was advised but was refused by the patient's cardiologist because of the risk involved.

Later a cholecystectomy was performed, without difficulty either during or subsequent to the operation. Within a year following the operation the patient was greatly improved in appearance. Occasional mild attacks of epigastric pain occurred for several years after operation but there have been no cardiac or digestive symptoms.

Case 2. Another instance of chronic cardiac and biliary tract disease relieved by operation:

A 49 year old man was seen in April, 1950. For several years there had been almost daily acute attacks of precordial distress which radiated down the left arm, somewhat relieved by nitroglycerin. The attack usually came on after the ingestion of fats or pastries. For 20 years fats and chocolate had sometimes caused nausea, abdominal pain and diarrhea.

In June, 1948, there had been a myocardial infarction. This diagnosis was confirmed by the electrocardiogram, which became normal in six months. In 1949 there had been an acute attack of pain suspected of being caused by a myocardial infarction, but the electrocardiogram remained normal.

On admission, physical examination was essentially normal. The cholecystogram revealed normal visualization with stones. The blood cholesterol was 358 mg. per cent. Tests of pancreatic and liver function were normal.

At operation, a chronic cholecystitis with cholelithiasis was found. There were many stones in the gall-bladder and in the cystic duct, which was partially occluded by an aberrant cystic artery. A cholecystectomy was performed. Cultures of the bile and gall-bladder wall were sterile.

Following operation the patient felt greatly improved. He was relieved of his anginal attacks and indigestion except for one acute attack of epigastric distress, nausea, vomiting and clay-colored stools, which followed dietary indiscretions three months later. The blood cholesterol is now 285 mg. per cent. The patient remains symptom-free.

Case 3. A physician relieved of both cardiac and digestive symptoms by cholecystectomy:

A physician, 45 years of age, was admitted November 21, 1950, with a history of one attack of biliary colic 18 years previously. For six months before admission the patient had been subjected to severe psychic trauma, and during this period he had severe distress and distention after practically every meal.

On admission the blood pressure was 200/125 mm. of Hg. Physical examination was otherwise normal except for tenderness in the right upper quadrant. The blood cholesterol was 324 mg. per cent. Liver function tests were normal.

At operation the gall-bladder wall was found to consist entirely of scar tissue, with many stones. A cholecystectomy was performed. Cultures of the gall-bladder wall and stones were sterile. The pathologic report was chronic cholecystitis. The delayed cholangiogram, taken 10 days after operation, showed no evidence of obstruction or lithiasis. The electrocardiogram, which preoperatively showed evidence of posterior myocardial infarction, became essentially normal after 10 days of common duct drainage.

Clinically, the patient has been entirely relieved of all symptoms following cholecystectomy. He has resumed his usual activities without difficulty. Following operation the blood pressure gradually subsided; it was 140/104 mm. of Hg on the sixth postoperative day, and has remained within normal limits except during periods of emotional tension.

Case 4. A patient who obtained temporary relief from anginal attacks following cholecystectomy:

A 62 year old man was admitted December 12, 1950, with acute attacks of precordial pain which had occurred from one to five times almost every day for two years. The attacks tended to occur with exertion or after heavy meals. There had been occasional attacks of epigastric pain. The patient had known that he had hypertension for 20 years.

On admission the blood pressure was 180/130 mm. of Hg. There was moderate cardiac enlargement. Abdominal examination revealed the liver edge 4 cm. below the costal margin.

The electrocardiogram revealed a left bundle branch block. The cholecystogram revealed no visualization of the gall-bladder. The gastrointestinal series was negative. The sedimentation rate and other laboratory examinations were normal.

The patient subsequently had a cholecystectomy elsewhere, at which time stones were found in the gall-bladder.

Following operation and a period of bed-rest (a previous period of hospitalization had not relieved the attacks), there were no anginal attacks for two months. Seven months after operation, following a few recurrent anginal attacks, the patient developed severe precordial pain with evidence of heart failure. He died six hours later in another hospital.

GROUP II

Case 5. A patient with a badly damaged heart, successfully operated upon and relieved of her digestive but not of her cardiac symptoms:

A 63 year old woman was admitted December 9, 1950, complaining of recurrent pains in the right upper quadrant of three years' duration, associated with belching, distention and an intolerance to fats. There had been repeated periods of excessive dyspnea, associated with hypertension, nervousness and apprehension. For seven months previous to admission there had been recurrent attacks of anginal pain, orthopnea and ankle edema. For 10 days previous to admission there had been a persistent pain in the right upper quadrant, associated with recurrent vomiting.

The past history included a luetic infection 25 years previously. The amount and character of antiluetic treatment could not be ascertained. Hypertensive cardiovascular disease had been known to be present for 15 years.

The cholecystogram had shown a large gall-bladder full of stones; the gastrointestinal series was negative. Cholecystectomy had been deferred previously because of cardiac failure. The blood Mazzini one year previously had been negative.

On physical examination there was tenderness in the right upper quadrant. The heart was enlarged, with a double murmur at the apex and a diastolic murmur over the aortic area and in the second to fourth interspaces to the left of the sternum. Laboratory examinations were essentially negative except for an icterus index of 17 units. The electrocardiogram showed a left bundle block with a QRS duration of 0.16 second.

At operation, a cholecystectomy was performed under ether anesthesia with no serious difficulties. The cultures of bile were sterile. The pathologic report of the gall-bladder wall was chronic cholecystitis.

Following operation the patient remained in a state of partial cardiac failure. The electrocardiogram remained unchanged. During a hospital re-admission for cardiac failure six months after operation, she was found to have a positive Wassermann. Clinical improvement and relief of cardiac failure followed the administration of 6,000,000 units of penicillin. There were no postoperative symptoms referable to the biliary tract.

This patient died two years later while in Florida.

Case 6. A patient with severe biliary tract and cardiac disease in whom repeated operations resulted in the relief of the biliary tract symptoms but not of those due to the heart.

A 48 year old Negro man was first seen in 1929 with an acute pancreatitis, acute appendicitis and chronic cholecystitis. An appendectomy, cholecystostomy and a drainage of the pancreas were done at that time. After having a biliary fistula for three months he was admitted for closure.

In 1936 the patient was re-admitted with right upper quadrant pain, jaundice, nausea, vomiting, chills and fever. At operation extensive adhesions were found. There was a perforation of the gall-bladder and an abscess cavity between the right

lobe of the liver and the hepatic flexure of the colon. The peritoneal cavity contained about 200 black gall stones and about 50 c.c. of free pus. A cholecystostomy and drainage were again performed.

Two years later the patient was again admitted with right upper quadrant pain of 25 days' duration, vomiting, chills, fever and a painful "lump" in the region of the operative scar. Re-operation revealed partial obstruction of the small intestine, an abscess of the abdominal wall and an acute phlegmonous gall-bladder containing several stones. A cholecystectomy was performed.

For the following 18 months the patient did well relative to his biliary tract. Repeated preoperative duodenal drainages had shown the presence of *Escherichia coli*, the same type of organism found in the gall-bladder wall and in the stones at the time of operation. Following cholecystectomy, repeated duodenal drainage bile cultures were sterile.

The electrocardiogram showed initially a left ventricular hypertrophy consisting of high voltage of the QRS wave, a depression of the ST segment and a negative T wave in Lead I. There was no essential change in these findings, either before or after the operations.

During the period of observation, hypertension developed with progressive symptoms of cardiac failure. Three years after cholecystectomy, the patient was in advanced cardiac failure with a blood pressure of 240/130 mm. of Hg. The liver was four fingerbreadths below the costal margin.

Our experience with other patients having similar conditions suggests the advisability of early cholecystectomy to remove an active focus of infection. This would have obviated the need of repeated operations, which were undoubtedly detrimental to the patient's general condition and to his heart as well.

GROUP III

Case 7. An unsuccessful operation upon a critically ill cardiac patient with an acute gangrenous gall-bladder:

A 68 year old woman was admitted in 1950. She was known to have had a myocardial infarction six years before. For six years she had been having repeated anginal attacks, most frequently after her evening meals.

For four days before admission there had been an acute pain in the right upper quadrant with nausea. During this period, treatment elsewhere consisted of penicillin and streptomycin. On physical examination the temperature was 102° F., and the liver three to four fingerbreadths below the costal margin. There were no clinical findings of cardiac failure. The electrocardiographic findings were suggestive of a recent posterior wall myocardial infarction.

At operation, the day after admission, the gall-bladder was distended, necrotic and gangrenous. Stones were found in the gall-bladder but not in the common duct. There were dense adhesions between the gall-bladder, duodenum and colon. The gall-bladder contained gray fluid, with the odor typical of gas-forming organisms.

A cholecystectomy was performed. Cultures of the gall-bladder bile and wall showed gram-negative rods. The pathologic report was acute purulent hemorrhagic cholecystitis. The patient died nine days after operation following an embolic obstruction of the left popliteal artery.

The above case illustrates the well known danger of operating upon a patient with severe arteriosclerotic cardiovascular disease during a period of acute myocardial infarction. In retrospect, the outcome of the operation might have been different had the operation been performed at the onset of

acute symptoms. A cholecystostomy might have been a preferable procedure.

Medical Considerations

The cases cited clearly indicate the need of a comprehensive investigation of the biliary tract in all cardiac patients having digestive symptoms. In those patients coming to operation for biliary tract disease the possibility of myocardial failure or recent myocardial infarction should be ruled out beforehand.

The rôle of the internist or cardiologist is of particular importance in the preparation of the cardiac patient for operation. Here the possible increased operative risk involved requires careful attention to hydration and electrolyte balance. Digitalization may be indicated. In seriously ill patients there should be a complete battery of liver function tests, particularly including the bromsulfalein retention test and the determination of cholesterol and cholesterol esters. With severe degrees of impairment of liver function, supportive treatment and liberal amounts of carbohydrates and proteins are essential. With evidence of liver failure, operation should be deferred whenever possible until an appreciable improvement in liver function can be demonstrated.

In general, obesity is not considered a contraindication to operation. Reducing diets should include at least 80 gm. of protein daily. Patients who have recently undergone a regimen of weight reduction may not tolerate operation well, and a period of readjustment is advisable. The continued supervision of the cardiac status of the patient is needed, especially at the time of operation.

Repeated or serial electrocardiograms are useful as a means of differentiating, during an acute attack of pain, between a myocardial infarction and biliary colic. The elevation in serum bilirubin sometimes found after an attack of biliary colic is also useful in differential diagnosis. In general, the electrocardiographic changes described as found with biliary tract disorders cannot be considered diagnostic of biliary tract disease. These changes may occur with only intrinsic cardiac pathology. This condition is suggested in those patients in whom there is no change in the abnormal cardiac findings following cholecystectomy.

Surgical Considerations

Indications for surgery are the presence of obstructive or infectious biliary tract disease. The most common findings are cholelithiasis, cholecystitis or cholangitis, with or without liver involvement.

Contraindications to operation are recent myocardial infarction or intractable heart failure. In the suspected presence of such conditions, acute disorders of the biliary tract call for a cardiac consultation. Whenever possible, operation should be deferred for several months. Failure to

observe these precautions will be followed almost invariably by immediate serious consequences or the necessity of surgical intervention later. . However, in the presence of complete biliary tract obstruction or suspected perforation with peritonitis or abscess formation, a palliative operation such as a cholecystostomy may prove to be a life-saving procedure.

At the time of operation the greatest care must be observed to prevent possible reflex disturbances of the heart, such as cardiac irregularities, shock or cardiac standstill. To prevent serious consequences there should be the utmost care in the handling of organs, as well as an anterior splanchnic block with local anesthesia.

In the postoperative period, overdistention of the biliary tract must be avoided. We have found that biliary hypertension can produce irregularities in cardiac rate and rhythm, arterial hypotension, shock and cardiac standstill. Surgical experience with many patients of this type has shown that these effects can be prevented at the time of operation by the insertion of a catheter in the cystic duct or by a "T" tube in the common duct. The performance of such a simple procedure is well repaid by the prevention of vomiting and the cardiac complications noted.

The importance of these precautions cannot be overemphasized, because biliary hypertension usually is present in the immediate postoperative period. In the absence of adequate common duct drainage, intraductal pressure is increased by operative edema, continuous bile secretion by the liver, lack of food stimulus to promote the flow of bile into the duodenum (a condition frequently aggravated by vomiting), and the use of morphine or other narcotics. Such medication experimentally can produce common duct sphincter spasm sufficient to resist a bile flow far beyond the secretory pressure of the liver. This effect can be prevented by the use of atropine sulfate.

Anesthetic Considerations

Operations upon the poor-risk patient demand the complete coöperation of internist, surgeon and anesthetist. Regardless of the anesthetic used, the fundamentals of good physiologic functioning must be understood and maintained throughout the period of surgical interference.

To evaluate anesthetic technics and agents most suitable for the patient with biliary tract disease, the following classification has been established: (1) mild cardiac disturbances with vague symptomatology and slight electrocardiographic changes; (2) moderate cardiovascular disease with evident coronary artery involvement; (3) serious cardiovascular disease with advanced electrocardiographic changes, myocardial infarction, cardiac failure or vascular collapse.

In Class 1, any agent or technic can be used with impunity. Those with which the anesthetist is most familiar are preferable. In the other classes the utmost caution and vigilance must be observed, especially for those patients in Class 3.

In premedication of the patient, the use of substances such as atropine is of prime importance. Narcotic agents are used only in amounts adequate for the relief of pain, because they increase the tone of the sphincter of Oddi. Barbiturates are employed to allay anxiety.

Inhalation types of anesthesia, either gases or volatile agents, are used in most of these cases. Cyclopropane is most frequently used, usually supplemented with small amounts of ether. Contraindications to this technic are the presence of myocardial irritability or explosion hazards. No one agent will satisfy all requirements, nor is any agent pushed to the extent that its administration would be detrimental. To facilitate surgical intervention, muscular relaxation is obtained not so much by depth of anesthesia as by the judicious use of small amounts of curare.

With operative cholangiography, nonexplosive anesthetics are used. Small amounts of intravenous thiobarbiturates are given to supplement nitrous oxide-oxygen. The intravenous barbiturates are discontinued after the cholangiography has been completed, and either cyclopropane or ether is administered in a closed-system. Relaxation is obtained by nerve block or curare.

In the critically ill patient with fever, sepsis or moderate to severe cardiac disease, a combination of technics is necessary. For example, regional anesthesia may be supplemented by light inhalation anesthesia. Here infiltrations with 2 per cent procaine hydrochloride of the common duct and/or celiac plexus are indicated.

Because of the hyperreflexic nature of the area in which surgery is being performed, there may be bizarre changes in the blood pressure and pulse. Hypotension may sometimes be relieved by decompressing a distended gallbladder or common duct. When hypotension is noted, the anesthetist advises the surgeon, who infiltrates with the local anesthetic agent noted. Following these procedures lighter planes of anesthesia may be sufficient.

Myocardial irritability of ventricular origin is controlled by the intravenous use of procaine or procaine amide in dosage of 100 to 500 mg. Changes such as hypotension with bradycardia of vagal origin may be controlled by the cautious intravenous use of atropine. With prolonged vomiting there may be an imbalance of sodium and/or potassium. This situation requires chemical blood studies and replacement where necessary. (Caution should be observed in patients deficient in potassium, as they do not tolerate curarizing agents well.) Fluid and blood loss during surgery are estimated and replaced.

Spinal anesthesia is usually well tolerated by patients who are good risks, but it is not always tolerated by those with poor myocardial reserve. If the intrathecal route is used, hypotension secondary to sympathetic paralysis may occur. Spinal anesthesia is rarely used for patients with poor myocardial tone, as they do not tolerate precipitous drops in blood pressure, which may not respond adequately to vasopressor substances. With a low

diastolic pressure, the coronary arteries are not properly filled. Other disadvantages of the use of spinal anesthesia are: (a) vagal reflexes may not be obviated; (b) adequate height of anesthesia depresses the tidal air volume; (c) supplementary inhalation or intravenous agents frequently must be used to relieve nausea precipitated by traction.

In conclusion: (a) The anesthetist should select the technics and agents with which he is most familiar. (b) The patient must be carefully evaluated preoperatively. (c) Preoperative vagolytic agents are indicated. (d) High concentrations of oxygen should be used with inhalation and regional technics. (e) Head-up position is indicated for heart failure as shown by pulmonary congestion. (f) Constant vigilance and caution are necessary.

Discussion

In the presence of both cardiac and biliary tract pathology, the results of operation are dependent upon the relative degree of pathologic changes in the heart and biliary tract. If the intrinsic cardiac pathology per se is advanced sufficiently to cause the symptoms and findings noted, no beneficial effects upon these conditions can be expected following cholecystectomy. If, on the other hand, cardiac pathology is less advanced and the extrinsic factor of stimulation from the biliary tract is responsible for the symptoms or other abnormal findings, surgical intervention should improve the condition.

Conclusions

1. Disorders of the biliary tract and cardiac disease are both present in many patients dying when over the age of 40.

2. Experimental and clinical investigations have shown that, in the patient with organic heart disease, pain and abnormalities in cardiac rate and rhythm may be induced by stimuli originating in disorders of the biliary tract.

3. In the patient with pain, indigestion or cardiac symptoms associated with digestive symptoms, there should be a comprehensive diagnostic investigation of both the heart and the biliary tract.

4. Evidence of a pathologic condition of the biliary tract may be an indication for surgery.

5. Myocardial failure or recent myocardial infarction is a contraindication to operation.

6. Elective operations upon the biliary tract in properly selected patients are usually well tolerated, provided there is careful and adequate supervision of the diagnostic investigation, and experienced personnel are available for surgical and anesthetic procedures.

7. The results of surgery are usually good in the relief of biliary tract

symptoms, provided the pathologic condition present has not progressed too far.

8. The relief of cardiac abnormalities can be expected only when they result from extrinsic cardiac stimulation rather than from intrinsic cardiac disease.

9. Since the relative degrees of cardiac and biliary tract pathology cannot be determined preoperatively with accuracy, the prognosis should be guarded.

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RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE OF RECENT YEARS

(TENTH RHEUMATISM REVIEW) *

Part I

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CONTENTS

PART I

General incidence of rheumatic diseases 499
Classification of diseases of joints and related structures 500
Diseases related primarily to trauma 502
Arthritis due to specific infectious agents:
Gonorrheal arthritis 505
Tuberculous arthritis 507
Syphilitic arthritis and synovitis 510
Yaws 511
Meningococcic arthritis 511
Suppurative arthritis 512
Typhoid arthritis 513
Brucellosis 514
Rat bite fever 516
Rarer forms of specific infectious arthritis 516
Mycotic diseases of joints 518
The adrenal cortex and rheumatic diseases 519
Rheumatic fever 529
Rheumatoid arthritis 549
Rheumatoid (ankylosing) spondylitis 590
Osteoarthritis 593
Backache and sciatica 598
Gout and gouty arthritis 609
The uric acid problem 615

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Part II of this Review and the complete bibliography will appear in the October issue of this Journal.

The last Review prepared by the Editorial Committee of the American Rheumatism Association was the Ninth; it concerned the American and English literature from 1941

Definition of "Rheumatism" and the "Rheumatic Diseases"

The terms "rheumatism" and "rheumatic diseases" are now properly used to refer to a large group of diseases of the musculoskeletal system, characterized by pain and stiffness of joints, muscles and related structures. These disorders affect the various articular structures (cartilage, joint capsule and bone), the connective tissue around joints and, in some instances, the fibrous tissues in a wide variety of organs.[336] Rheumatism was a collective term for illnesses in which pain in or about joints was a prominent symptom.[616] An interesting addition to the history of rheumatism in the eighteenth century was made by Copeman.[347]

General Incidence of Rheumatic Diseases

Social and Economic Importance

The high incidence of rheumatism among civilians was emphasized by many writers.[184, 319, 333, 533, 652, 1272, 1372, 1488, 1487, 1642, 2000] Among the chronic diseases, rheumatism ranked first in incidence and second only to nervous and mental disorders as causes of disability.[2000] It was estimated that in the United States more than 300,000 persons are made unemployable by rheumatic diseases annually, and more than 147,000 are rheumatic invalids[1372]; and that the diseases accounted for more than 92 million days lost from work per year, representing an economic loss of a half-billion dollars per year.[1460a] In a U. S. Army General Hospital, 3.6 per cent of 5,524 cases admitted to the medical service had "arthritis or allied disorders."[666] Reports from various U. S. Army Hospitals in the Mediterranean theater showed the incidence of arthritis to be about 3 per cent, with an equal number of patients with rheumatic symptoms without evident arthritis.[1827]

In Denmark, chronic polyarthritis was responsible for 6 per cent of the persons granted disability benefits.[1483] Of 93,750 sickness reports from insurance companies in Switzerland, arthritis represented 16.2 per cent of all diseases, an incidence exceeding that of tuberculosis by a ratio of 36 to 1.[184] Among the personnel of the Swiss Federal Railways, arthritis accounted for 16.4 per cent of the total absence from work.[184, 1816]

In Scotland during the year 1937–1938, there were over 45,000 new cases of incapacitation from rheumatism in the insured population of 1,837,000.[583] In two localities in Scotland, 7.0 per cent[1477] and 9.4 per cent[885] of all visits for medical care were because of rheumatism. It was calculated that one in 50 insured men and one in 60 insured women were incapacitated for one month of each

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through 1945, and was published in the Annals of Internal Medicine, Volume 28, January and February, 1948. This Tenth Review is concerned with the literature from 1946 through 1950. The editorial comments express the opinion of the authors of the Review, the Editorial Committee, and are not necessarily those of the Association.

The initiation of the Rheumatism Reviews and their continued appearance since 1935 have been possible chiefly because of the energy and devotion of Dr. Philip S. Hench. The preparation of the Tenth Review was begun under his chairmanship, and its completion could not have been accomplished without his advice and assistance. In recognition of his enthusiasm and service as the moving spirit behind the initiation and continuation of the Reviews, the Editorial Committee and the American Rheumatism Association dedicate the Tenth Rheumatism Review to Dr. Philip S. Hench. It is particularly appropriate that the Tenth Review, which includes the outstanding discovery of the antirheumatic effects of cortisone and corticotropin by Dr. Hench and his colleagues, should be so dedicated.

year by "muscular rheumatism," or six weeks of each year by "neuritic rheumatism." [504] From a survey in 1947 of 25,000 households across Canada, it was estimated that about 7 per cent of the total adult population were afflicted with arthritis or rheumatism in some form.[1642]

In Great Britain, 7 per cent of the population were incapacitated by rheumatism for at least one day each year, and half of the population suffered from rheumatism which was not disabling.[323] It was estimated that these diseases cause one sixth of the total industrial disability and account for one sixteenth of all funds paid out by that country for pensionable invalidism. Rheumatism accounted for the loss of 3,000,000 work weeks and 7 per cent (£17,000,000) of the total sum paid for sickness and disability benefits.[345] In 1941, loss of income from rheumatic diseases in England and Wales was reported to be £25,000,000.[1695] [These figures would be much higher in our present-day inflationary values.—Ed.] In Sweden, reports from practitioners in 1943 indicated that 61,000 persons (1.5 per cent of the population) visited physicians for rheumatic diseases, and that 46 per cent of these needed hospitalization.[905]

Classification of Diseases of Joints and Related Structures

No classification of the rheumatic diseases can be entirely satisfactory while the etiology of the various diseases in this group remains unknown.

The classification of the rheumatic diseases recently used [319, 472] has been, with few exceptions,[828] that adopted in 1941 by the American Rheumatism Association (Ninth Rheumatism Review). Some adaptations of this classification were recommended in the interest of simplification, descriptive clarity, and more accurate differential diagnosis.[836, 601, 1372, 1558, 1642] The 1949 *Primer on Arthritis* [836] divided the more common rheumatic diseases into seven important groups: (1) arthritis due to known microbial agents, (2) the arthritis of rheumatic fever, (3) rheumatoid arthritis, (4) degenerative joint disease, (5) arthritis due to direct trauma, (6) arthritis due to gout, and (7) the nonarticular forms of rheumatism.

Relative Frequency of the Rheumatic Diseases

A survey was conducted in a civilian community of Scotland which allowed the incidence of the various types of rheumatism to be assessed. Those reported during November, 1945, appear in table 1; similar distribution was observed in March, 1946.[1477] A relatively high incidence of nonarticular rheumatism in Britain is evident, as noted in previous years. In a typical Scottish county of mixed industrial and rural population of 65,500 persons, the number of hospital-treated patients in one year was distributed among the rheumatic diseases as follows: acute rheumatic fever, 13; fibrositis, 146; arthritis, all forms, 163; diseases of ligaments, 34; internal derangement of knee joint, 52; and bursitis and synovitis, 62.[533]

The relative incidence of rheumatic diseases at two United States Army Rheumatism Centers during World War II [852] and in a United States Army General Hospital which was not a rheumatism center is shown in table 2. In the United States General Hospitals in the Mediterranean Theater, 40 per cent of the rheumatic patients had arthralgia and psychogenic rheumatism, 25 per cent had rheumatoid arthritis, 25 per cent had osteoarthritis, and less than 10 per cent had specific infectious arthritis.[1527]

TABLE I

Types of Rheumatic Diseases Reported from Kilmarnock, Scotland, during November, 1945[1477]

	Males			Females			Total
	Under 15 Years	15 to 65 Years	Over 65 Years	Under 15 Years	15 to 65 Years	Over 65 Years	
Population at Risk	5,276	12,000	1,790	5,295	13,524	2,115	40,000
Acute Rheumatism	—	3	—	2	3	—	7
Subacute Rheumatism	2	14	1	2	17	1	37
Articular:							
Rheumatoid Arthritis	—	23	1	—	29	6	59
Osteoarthritis	—	7	7	—	13	5	32
Nonarticular:							
Muscular Rheumatism	5	154	6	3	131	10	309
Neuritic Rheumatism	—	53	4	1	56	7	121
Total New Cases	7	254	19	7	249	29	565

The distribution among the first 100 cases of "rheumatism" admitted to a British general hospital in France during World War II was: rheumatic fever, 15 per cent; rheumatoid arthritis, 6 per cent; osteoarthritis, 9 per cent; fibrositis, 70 per cent.[846] Among British forces in the Middle East, 2.5 per cent of admissions to Army hospitals during 1943–44 were for "rheumatic diseases," of which "fibrositis" made up the largest number. The relative incidence of rheumatic diseases in British Emergency Medical Service Hospitals is shown in table 3.[245] [The high incidence of "fibrositis" may be explained in part by the fact that no separation was made among the different forms of nonarticular rheumatism, including psychosomatic disorders—all were designated as "fibrositis."—Ed.]

Of 500 consecutive admissions to the rheumatism service of a U. S. Veterans Administration Hospital, 41 per cent of the patients presented evidence of articular involvement or arthritis; 28 per cent had nonarticular rheumatism, embracing the various

TABLE II

Relative Frequency of Various Rheumatic Diseases

Group A—among the first 1,000 consecutive admissions to a United States Army Rheumatism Center (Army and Navy General Hospital)[668]

Group B—among the first 800 completed cases at another United States Army Rheumatism Center (Ashburn General Hospital). Hench[668]

Group C—among 200 cases admitted to a United States Army General Hospital (not a Rheumatism Center). Goldstein[666]

	Group A (1,000 Patients) Per Cent	Group B (800 Patients) Per Cent	Group C (200 Patients) Per Cent
Rheumatoid Arthritis	33.1	38.3	32.0
"Psychogenic Rheumatism"	20.0	16.1	—
Osteoarthritis	13.6	26.7	40.0
Fibrositis*	13.4	2.2	17.0
Specific Infectious Arthritis	1.3	1.6	0.5
Gouty Arthritis	1.0	0.6	1.5
Miscellaneous Conditions	13.5	14.5	8.5
Unclassified	4.1	—	0.5

* Intramuscular or periarticular, or both; bursitis, tendinitis, etc.

types of fibrositis; 7 per cent had "psychogenic rheumatism," and 24 per cent had a variety of diseases unrelated to the musculoskeletal system. There were 207 patients with objective evidence of "arthritis"; of these, 48 per cent had rheumatoid arthritis, 36 per cent had osteoarthritis, 2 per cent had infectious arthritis, 7 per cent had gout, 5 per cent had rheumatic fever and 1 per cent had a Charcot joint.[616]

TABLE III

Incidence of Rheumatic Diseases in British Army Hospitals in Emergency Medical Service[341]

	Per Cent	
	Officers	Other Ranks
Subacute Rheumatism	4	4.5
Fibrositis	35	52.5
Lumbago	—	4.5
Sciatica	15	12.3
Rheumatoid Arthritis	19	19
Osteoarthritis	6	1.3
Spondylitis	9	1.1
Synovitis	—	2
Pes Planus	—	1.5
Gout	5	0.4
Other Diseases	7	0.9

It was estimated that in the United States the distribution of rheumatic diseases in 100 patients who suffer from rheumatism sufficiently to make them consult a physician would be approximately as follows: One with rheumatic fever; two with gonococcic arthritis; three to five with miscellaneous forms (tuberculous arthritis, arthritis with ulcerative colitis, Charcot's joints, etc.); three to five with gout; seven to 10 with traumatic arthritis; 10 to 20 with nonarticular rheumatism; 25 to 30 with degenerative joint disease; and 30 to 40 with rheumatoid arthritis.[336]

DISEASES RELATING PRIMARILY TO TRAUMA

Joints can be damaged by (1) a single acute injury or (2) chronic injury from minor repeated trauma or microtrauma. The limited capacity of articular cartilage for regeneration and healing was emphasized as an important contributing factor to the late results of trauma.[731]

Lesions Produced by Acute Trauma. Any one or several components of the joints and neighboring structures may be affected; the dominant injury may be a capsular or ligamentous tear or stretching, contusion of synovia or juxta-articular bursa, meniscus tears or detachments, or splitting or detachment of articular cartilage. Hydrarthrosis, particularly common in the knee, results from contusion of the synovia.[1914] It can usually be readily recognized clinically, and the roentgen findings have been carefully described.[67] When the effusion is bloody, aspiration is recommended to minimize a deleterious effect on cartilage. In clinical and experimental studies Soeur [1879] found that effusions of blood in the joint produced an immediate intense proliferative reaction in the synovial membrane which was temporary and regressed rapidly. Lipohemarthrosis with layering of fat and blood in the knee joint was described in association with intra-articular fracture.[1811]

Penetrating or perforating wounds of the joints were best treated by early surgical removal of damaged tissue and instillation of penicillin.[315] Good results were reported in 40 or 42 patients with "traumatic arthritis" treated with intravenous procaine.[704] [Data do not indicate whether these were related to single acute injury or to late results of trauma.—Ed.]

Late Results of Trauma. When articular cartilage is damaged, continued use of the joints, or the impinging of a loose or partially detached body on the articular surface, may eventually lead to late secondary traumatic osteoarthritis. Ghormley emphasized the importance of correcting internal derangements of the knees in order to prevent this development.[636] Hallux rigidus, a painful condition of the great toe with loss of dorsiflexion of the first phalanx, was found to have the pathologic characteristics of a traumatic synovitis followed by early development of osteoarthritis.[152]

Repeated and chronic trauma can also be responsible for diseases of bursae, tendons and ligaments. Involvement of the calcaneal tendon from marching in ill-fitting or partially worn-out boots was described.[200] In addition to the well known occupational types of such extra-articular lesions, there were reported "boxer's bursitis" of the metacarpo-phalangeal bursa,[2124] ossifications in the tibial collateral ligaments associated with the chronic strain of roller skating,[1118] calcareous peritendinitis of peroneal tendons related to the use of narrow-runged ladders by house painters,[1396] and calcification in the anterior ankle ligaments of professional soccer players.[1360]

Good results followed treatment directed at eliminating the trauma, rupture of traumatic bursae or, when necessary, surgical excision. The rôle of trauma in the etiology of Baker's cyst was discussed.[838]

Special Locations. *Temporomandibular Joint.* In a detailed study of the anatomy, physiology and pathology of this joint, Markowitz and Gerry [1294] reported the causes of abnormality in 103 patients as: malocclusion, 36; dislocations, 14; other traumatic conditions, 35; referred pain, six; other types of arthritis, 12. The importance of malocclusion in producing osteoarthritis in this joint was indicated by several reports.[87, 124, 566, 718] Of 185 cases of temporomandibular arthritis, 17 per cent were related to an immediate single trauma, 18 per cent were due to rheumatoid arthritis, and the remainder were osteoarthritis related to malocclusion.[242] Appropriate dental correction relieved symptoms in all but 0.5 per cent of patients. Post-traumatic effusion of the temporomandibular joint was complicated by otitis media.[487]

Acute trauma, usually a direct blow on the chin [432, 1202, 1972] or war wounds,[282] ranked with infection, such as suppurative otitis media,[1488] as a cause of ankylosis of this joint. Of 18 cases, six were related to trauma, four to infection and eight to rheumatoid arthritis.[2048] Surgical correction was recommended with resection of the condylar neck and, if necessary, the coronoid process.[432, 1202, 1819, 2048]

Patella; Chondromalacia and Osteoarthritis. The reaction of patellar cartilage to repeated stress, strain, pressure or disturbed joint mechanics was described as local softening, gradual unmasking of vertical fibrils, loss of hyaline matrix with early fissuring or splitting, followed by three types of changes: (1) rapid disintegration of all or part of the articular bed (chondromalacia), (2) local cartilage fracture or osteochondritis dissecans with separation of a large cartilage fragment, or (3) gradual thinning of entire articular cartilage with erosion down to bone.[201] Of 12 patients with chondromalacia, symptoms were precipitated by recurrent strains of the knee in five and by repeated direct blows on the patella in six. In a series of 50 patients, a

history of direct trauma to the patella was obtained in 27.[1907] Pathologic and clinical features were described [291, 705, 1839]; symptoms and signs helpful in the diagnosis were intermittent pain over anterior aspect of the knee with momentary sensation of catching, transient effusions and stiffness, crepitation on active movement of patella, atrophy of thigh, and tenderness over medial and articular surface of the patella. In mild cases, physical therapy and avoidance of trauma to the knee were recommended. In moderately severe cases, surgery was followed by relief of symptoms and restoration of function. Some authors favored resection of disintegrating cartilage only, with patellaplasty when necessary,[224, 291, 635] while others regarded patellectomy as the treatment of choice.[933, 1819] [Undoubtedly more attention should be directed to recognition of patellar pathology as a cause of disability in the knee joint.—Ed.]

Internal Derangements of the Knee. The knee is especially prone to numerous injuries, which were described.[256, 362, 464, 1003, 1412] Acute instability of ligaments was observed in paratroopers, which in 59 of 85 cases resulted from injuries to the tibial collateral ligament produced by severe abduction of the knee when the leg was caught in the suspension lines of the parachute. Treatment emphasized immediate immobilization in plaster and early intensive exercise of the quadriceps femoris muscle. The degree of atrophy of the quadriceps proved to be the most reliable criterion of functional results, which were excellent in 95 per cent of the abduction injuries. Calcification of the tibial collateral ligament was a frequent but nondisabling complication.[1077]

The effects of meniscus injury on the synovial membrane, as observed in patients and in experimental animals, were minimal during the first few weeks, with formation of villi and stratification of intima after the first month and then progressive sclerosis, with persistent and more intense fibrosis after several months.[1879] Ghormley [636] considered the changes in articular cartilage which occur after removal of a torn meniscus to be minimal compared to those which occur if the damaging element is allowed to remain in the knee. He also called attention to the superior end-results of surgical removal of torn semilunar cartilages in civilian practice as compared with military experience.[635]

In 14 patients with knee joint derangement, the essential lesion was inflammatory hyperplasia of the fat pad, attributed to repeated low grade trauma. Diagnosis was substantiated at operation.[1916]

Contrast radiography with air [185, 843, 1066] or opaque media [1016] was found to be helpful in the diagnosis of knee lesions. An evaluation of pneumo-arthrography in 315 patients in whom the diagnosis was established at operation showed the procedure to be of special value in the diagnosis of abnormal menisci, fat pads and bursae; roentgenographic findings were confirmed in 81.6 per cent of the cases.[1370]

Pellegrini-Stieda Disease. The disputed and probable multiple nature of this condition, characterized by para-articular calcification at the medial aspect of the knee joint, was considered in detail in the Ninth Review. There has been no further clarification as to whether this represents calcareous tendinitis, calcareous bursitis, calcification of medial collateral ligament or some other lesion. Eight cases were found in 9,218 examinations in an Army General Hospital. All gave a history of injury, occasionally a single violent episode but more often repeated minor trauma. The calcification was attributed to subperiosteal hemorrhage and metaplasia of the medial collateral ligament. X-rays were diagnostic, revealing calcification just medial to the inner condyle of the femur. An evolutional type appearing as a hazy or fuzzy opacity was distinguished from the stabilized form with a dense, sharply outlined shadow. Surgical excision was advised if there was clinical discomfort, but only when the process had reached the stabilized form.[1743]

Sprains and Strains. More than half of 51 severely "sprained" ankles were shown to be actually subluxations, 23 of which were spontaneously reduced and four

recurrent. The anterior talofibular ligament was found to be the important component of the fibular collateral ligament, and special x-ray views were recommended in severe ankle sprains.[1192] Quigley[1606] emphasized the importance of immediate treatment with cold, compression, rest and elevation, and had discarded the use of novocain because of unsatisfactory results. The greatest value of novocain was felt to be in the matter of diagnosis, enabling the surgeon to classify cases as major or minor injuries.[1576]

"Tennis Elbow" (Epicondylitis, Radiohumeral Synovitis). This syndrome of pain over the outer side of the radiohumeral joint on grasping or pronating results not only from sports but also from occupations necessitating strong hand grasping and compound forearm movements. Similar symptoms can apparently be produced by different pathologic lesions in this region: an adventitious bursa,[947] incomplete tear of extensors at their origin from the epicondyle,[1368] traumatized synovial fringe or radiohumeral fold,[1162, 1913] and epicondylar periostitis. The absence of satisfactory microscopic pathology[1364] was reported. In two series, about 84 per cent of the patients were men.[1364, 2009] Treatment was adapted to the severity and duration of symptoms, progressing from heat, massage and splinting in mild cases, through x-ray therapy, novocain injections or manipulation in more severe cases, to surgical treatment.[25, 1913] Treatment by heat, massage and rest was successful in 20 of 22 patients, by manipulation in 31 of 40, by x-ray in two of four, and by surgery in all of nine.[2009]

Secondary Influence of Trauma on Articular Disease. Jonsson and Berglund[1012] reviewed the relationship of trauma to rheumatoid arthritis. In 2,236 cases of rheumatoid arthritis, they found 12 with a history of trauma, but only one case fulfilled rigid criteria for a causal relationship. Gout occurred in less than 1 per cent (38 out of 4,500) of consecutive industrial accident cases.[1103] As an industrial problem, the relationship of trauma to osteoarthritis, particularly osteoarthritis aggravated by trauma, is by far the most frequent and most troublesome.[768, 1646, 2202] Wolff[2202] analyzed 162 compensable arthritis cases, finding only 10 per cent diagnosed as positively nondegenerative. Incapacitation resulted from minor accidents and was out of proportion to the degree of injury; time lost from work averaged 122 days. In another series of 85 patients with osteoarthritis aggravated by trauma, a total cost of over $52,000 was involved in their management.[768]

Arthritis Due to Specific Infectious Agents

Gonorrheal Arthritis

Since the introduction of sulfonamide and antibiotic therapy for genital gonorrhea, gonorrheal arthritis has become a disappearing disease.[1829] The incidence of gonorrheal arthritis per 100,000 admissions to the Mayo Clinic has fallen from 45 in 1937 to two in 1945.[844]

Clinical Data. Multiple joints were affected in 80 per cent of 202 cases of gonorrheal arthritis. Most frequently involved were the large joints (especially knees and ankles), and less frequently the joints of the hands and feet. Relatively infrequent sites were the intervertebral, sternoclavicular and temporomandibular joints. Fifty-four per cent of the patients in this series were male.[1696]

Three women with acute polyarthritis, fever, tachycardia and electrocardiographic changes indicating myocarditis were believed to have acute rheumatic fever. Diagnosis of gonorrheal arthritis was finally established by x-ray evidence of a destructive arthritis, a positive cervical culture or gonococcal complement-fixation test, and the

response to sulfonamides or penicillin. A fourth woman with gonorrheal arthritis also revealed T-wave changes "typical of acute rheumatic fever." The electrocardiographic changes were attributed to a toxic myocarditis.[1615]

A total of six patients with keratosis blennorrhagica (five had arthritis) was reported.[592, 1386, 1825, 2051] In one patient, gram-negative diplococci were present in the biopsy of cutaneous lesions.[1386] [It appears that some of these patients may have had the cutaneous lesions of Reiter's syndrome rather than keratosis blennorrhagica associated with gonorrheal infection.—Ed.]

Laboratory Data. Cultures were the most reliable method of diagnosis for gonococcal infection and the best criterion of cure. The most satisfactory culture medium was Difco Proteose Peptone No. 3 agar enriched with hemoglobin or laked horse blood.[1528, 2050] Carbohydrate confirmation and penicillin tolerance tests were useful to check suspected penicillin-resistant gonorrhea.[1528]

A positive gonococcus complement fixation test was of questionable diagnostic value in genital gonorrhea, but was thought to be more reliable in the diagnosis of gonorrheal arthritis; it was positive on the blood or joint fluid in 82 per cent of 99 patients.[1696]

Differential Diagnosis. In view of observations of electrocardiographic changes in acute gonococcal arthritis, the combination of electrocardiographic abnormality and polyarthritis can no longer be accepted as pathognomonic of acute rheumatic fever.[1615] The necessity for specific treatment based on prompt diagnosis, with emphasis particularly on aspiration and culture of synovial fluid, was demonstrated in three patients in whom permanent joint disability developed during the period they were being treated for rheumatic fever. [In recent years, gonorrheal arthritis is more often seen in women, and frequently is initially confused with acute rheumatic fever. This is undoubtedly a reflection of the increased difficulty in diagnosis of genital gonorrhea in women.—Ed.]

Most "penicillin failures" in gonorrheal arthritis were attributed to failure to differentiate this disease from rheumatoid arthritis, nonspecifically reactivated by genital gonorrhea. [See section on Relation Between Rheumatoid Arthritis and Other Diseases. —Ed.]

Treatment of Gonorrheal Arthritis. The changing nature of treatment during the last 20 years was reviewed.[1696, 1902] The first major advance over symptomatic and supportive treatment was the introduction of fever therapy in the early 1930's. This was followed by the introduction of the sulfonamides, which in turn were supplanted by penicillin. During the later years of sulfonamide therapy the cure rates for genital gonorrhea decreased; in one study the recovery rates for gonorrheal arthritis were fairly well maintained during these years, but with a definitely longer period of administration and larger total dosage of the sulfonamides.[1696]

While penicillin was regarded as the treatment of choice,[844, 1590] a few patients had been cured with other methods: sulfathiazole[1590] and spinal pumping by the Speransky method.[22] [The rationale of the latter is dubious.—Ed.] Success was reported using combined therapeutic efforts: 28 of 30 soldiers with presumptive gonorrheal arthritis returned to duty following sulfathiazole combined with systemic and intra-articular penicillin (Phinney, reported by Short[1829]); 235 of 300 presumptive cases were cured by combined cabinet hyperthermia and penicillin[882]; fever therapy was combined with either sulfathiazole or penicillin; and streptomycin was followed by penicillin.[1283] [Much of this published work defied analysis because of inadequate data on diagnosis, treatment and results.—Ed.]

Penicillin in Gonorrheal Arthritis. In only three papers was sufficient information furnished to permit critical appraisal of results of penicillin therapy, where

criteria for proved or probable diagnosis were stated and penicillin was the only therapeutic agent.

It is necessary to use more intensive and more prolonged administration of penicillin than is required to clear up the genital infection. Of 17 cases of gonococcal arthritis proved by positive smears or cultures of joint fluid, 15 were acute and of less than one month's duration. The first seven of these were treated with penicillin over eight to 30 hour periods, in total dosage usually less than 1,000,000 units; the genitourinary infections cleared promptly but there was no improvement in the arthritis. The next eight acute cases received 1,000,000 to 2,000,000 units of penicillin over a period of five to 10 days; in all cases there was complete recovery of joint function.[890]

Experience in 202 probable or proved cases treated by various methods from 1936 through 1947 was reported. Treatment with the Kettering hypertherm resulted in recovery of 21 of 33 patients (64 per cent), with better results in patients treated within the first 30 days of joint involvement. Intravenous typhoid vaccine gave inferior results in 22 patients, and in no case was it considered adequate. Sulfonamides were used in 140 patients, with favorable results in 97 (69 per cent). Penicillin was given to 32 patients, of whom 23 recovered (72 per cent). Of 27 in whom penicillin dosage and duration were considered adequate, recovery occurred in 23 (84 per cent). In both sulfonamide and penicillin-treated groups, long duration of joint involvement before initiation of treatment did not exert so unfavorable an influence on outcome as did the existence of previous episodes of arthritis.[1898]

Favorable results were obtained in 23 of 28 (82 per cent) proved or presumptive cases in which the total doses of penicillin ranged from 500,000 to 9,000,000 units over periods of from four to 30 days. In every one of these 28 cases, including the five regarded as failures, systemic and local acute manifestations of inflammation were controlled and there were no instances of progression; "bacteriologic cure" in every case was inferred. The patients regarded as failures showed residual joint deformities or chronic joint inflammation. "Earlier judicious use of joint motion and other physiotherapeutic modalities as a supplement to penicillin therapy" was recommended.[1909]

There were no reports of penicillin resistance in cases of gonorrheal arthritis. In genital gonorrhea, most authors reported no evidence of natural penicillin resistance.[436, 1187, 1528, 2050] However, 24 cases of mild resistance [462] and four cases of extreme resistance [884] were well documented.

Penicillin appeared to be the treatment of choice in gonorrheal arthritis because its results are at least equivalent, if not superior, to other methods, and because of its low toxicity and ease of administration. Usual adequate dosage was 800,000 to 1,000,000 units daily for a period of 10 days. Intra-articular injections were usually not required [890, 891] but were occasionally used if no improvement resulted after three or four days of adequate intramuscular treatment. Because of technical difficulties and inherent dangers, fever therapy should be reserved for resistant cases.

Tuberculous Arthritis

Incidence. The incidence of tuberculosis of bones and joints has been declining in the United States [836] and in Great Britain.[1285] In 1947 there were about 400,000 cases of tuberculosis in the United States, of which approximately 16,000 had musculoskeletal involvement.

Clinical Data. Accepted clinical features of tuberculous lesions of joints, including the spine, were reviewed.[211, 737, 1328, 1525, 1744, 1746, 1859] It is of the utmost importance to remember that tuberculosis of a joint is a manifestation of a general infection. The need for a careful general examination to seek out a primary focus of tuberculosis elsewhere in the body was again emphasized.[211, 1372] The prognosis of tuberculosis of bones and joints is influenced by the presence of tuberculosis elsewhere in the body; associated pulmonary lesions are most important, genitourinary involvement next, and other skeletal lesions of least significance.[2168]

Diagnosis. The diagnosis was not always easy, and some of the common difficulties were emphasized.[1746, 2084] The slow onset of monarticular affection of the spine, hip or knee should suggest tuberculous arthritis. Seven cardinal clinical signs were listed as ill appearance, localized pain, swelling of the joint with spasm and deformity, muscle atrophy, slight temperature, abscess formation, and x-ray evidence of bone destruction.[1285]

In addition to the need for complete studies, including persistent search for tubercle bacilli,[85] several special procedures were discussed. X-ray tomography was described as a better means of visualizing tuberculous lesions of the involved joints.[1859, 2214] Repeated examination of fasting gastric contents for tubercle bacilli was said to be of value in orthopedic cases; the organism was found in the gastric aspirations in seven of 22 proved cases of tuberculosis of bones and joints.[85] Biopsy of regional lymph nodes was also considered helpful. In 100 consecutive cases a higher incidence of tuberculous adenitis was found in patients with early disease (71 per cent), as compared with those having clinically proved tuberculosis (56 per cent).[48] Warning was again given that in osseous tuberculosis the erythrocyte sedimentation rate may be normal or only slightly elevated.[48]

Special Localization: Clinical Data and Treatment. *Spine.* This was the most common site for tuberculous arthritis, comprising 0.4 per cent of 287,000 cases of tuberculosis of all types.[1328] Occasional difficulty in clinical diagnosis of Pott's disease was again encountered. Aids in differentiating tuberculosis from pyogenic osteomyelitis of the spine included recognition in the former of slower progress, longer duration of illness, greater destruction of intervertebral discs, and less osseous reaction with production of new bone.[737] In tuberculous spondylitis the early narrowing of the intervertebral joint space must be differentiated from a prolapsed vertebral disc, osteochondrosis and pyogenic infections.[1746] Various mechanisms by which tuberculosis of the spine can produce paraplegia were analyzed; most cases can be attributed to abscess formation, to mechanical accidents such as vertebral collapse, or to thrombosis.[1795] Unilateral paraspinal abscess may complicate tuberculosis of the spine.[1750]

Clinical healing of the tuberculous process in the spine in several cases coincided with the roentgenographic appearance of spontaneous fusion of the anterior spine.[738] The history and advantages of therapeutic fusion were reviewed.[2012] In an Australian study, immobilization alone resulted in solid fusion in 29 of 50 attempts; 12 of 15 attempts to fuse the spine surgically were successful.[1297] Of the patients (10 per cent) who did not get well with good nonsurgical care and were considered hopeless, decompressive laminectomy was performed with good results in three of 15 adults and in five of eight children.[411]

Hips. Clinical, roentgenologic and statistical studies of patients with tuberculosis of the hip were reported.[15, 211, 436, 728, 1329, 1589, 1744, 1996] The importance of early recognition was again emphasized. Tuberculosis of the hip joint is always destructive of bone, in contrast to tuberculosis of the knee, which sometimes is confined to the synovium.[1091] Limitation of motion is the earliest sign of tuberculosis of the hip and

often precedes roentgenographic evidence of disease.[1127] Clinical tests may help to differentiate tuberculosis of the hip from congenital dislocation, pseudocoxalgia and slipped femoral capital epiphysis.[1127]

Methods of treatment were evaluated by several.[15, 435, 1081, 1329, 1547, 1589, 1996, 2169] Immobilization alone resulted in complete bony ankylosis in 28 of 47 attempts; in 20 cases subjected to arthrodesis, complete ankylosis was obtained in 10 and partial ankylosis in five.[1297] Secondary changes, including shortening of the extremity, commonly followed prolonged immobilization of the tuberculous hip, regardless of the method employed.[1081, 1329] Opinions varied as to the choice of surgical procedures to obtain fusion of the hip.[192, 211, 1329, 1547, 2169]

Greater Trochanter and Bursa. Two cases of tuberculosis of the greater trochanter and its bursa were added to the 105 summarized by Wassersug in 1940.[987] Infection usually originated in the bursa. Treatment by early and adequate excision of all infected tissue was considered best. Tuberculosis of the subdeltoid bursa without involvement of bone was cured by excision, drainage, immobilization and general hygienic care.[1064]

Other Joints. Tuberculosis in the shoulder joint followed the same course as in other joints more commonly affected.[269] A new method for arthrodesis of the tuberculous elbow was described.[630] Tuberculous dactylitis was most frequently seen in children, as a complication of primary tuberculous infection, and prognosis for complete healing of bone was excellent provided the patient survived other manifestations of the tuberculous infection. Bones of the hand were involved eight times more often than those of the feet.[632, 778] One case of proved tuberculous dactylitis in an adult (a rarity) was reported.[2028] Sacroiliac tuberculosis has been regarded as rare; however, 22 cases were admitted to Royal Hobart Hospital in Tasmania during a 12 year period.[1525]

Streptomycin Therapy. Without exception, the experience of all authors indicated that the results of surgical treatment of bone and joint tuberculosis were improved by the use of streptomycin, alone or in combination with para-aminosalicylic acid.[147, 192, 220, 308, 401a, 919, 1328, 1405] In cutaneous draining sinuses excellent results were reported. In 12 patients, only one sinus remained patent after four months, most of them closing within four weeks of the start of treatment,[220] in a series of 11 patients, 74 per cent of the sinuses healed within three months.[401a] The drug was a valuable adjunct in the treatment of spinal, hip and shoulder joint tuberculosis, but it was not considered a substitute for surgery.[308, 1328, 1391, 1405] The use of this antibiotic represented a tremendous advance in the treatment of tuberculous arthritis when combined with surgical excision of diseased tissues or with arthrodesis, and "undoubtedly made possible operations in cases much earlier than otherwise could be done."[985, 1661]

[The dosages reported have varied greatly. At Fitzsimons Army Hospital, 2 gm. of streptomycin every other day, in conjunction with 12 gm. of para-aminosalicylic acid daily, are routinely used. There is no longer a question as to whether streptomycin is beneficial in the treatment of musculoskeletal tuberculosis. As in pulmonary tuberculosis, its use in combination with para-aminosalicylic acid is clearly indicated.—Ed.]

General Remarks on Treatment. Disagreement continued regarding the value of surgical treatment to obtain fixation. The opinion was expressed that bone grafts greatly improve results of treatment in the spine and hips in adolescents and adults, but in children bone grafts were useful only in hip involvement.[1890] Results in 253 patients with tuberculosis of the knee indicated that conservative and surgical treatments have to supplement each other.[1106] Diasone

was useful as an adjunct in the treatment of tuberculosis of bones and joints in 18 children.[289] The effect of cortisone in two patients with tuberculosis involving the knee was studied.[175] [Its use is not recommended in tuberculous arthritis.—Ed.]

"Tuberculous Rheumatism" (Poncet's Disease) and Nondestructive Tuberculous Polyarthritis

In two British [1817, 2218] and three American articles [674, 1372, 1803] the interesting and puzzling concept of nondestructive "allergic" synovitis resulting from nonarticular tuberculosis was discussed. Eight cases were reported in which rheumatism occurred in the course of tuberculosis, usually in the lungs. It was suggested that rheumatic manifestations in the course of active tuberculosis might indicate spread of infection.[1803] The numerous degenerative and inflammatory extrapulmonary lesions which are "clinically tuberculous" cannot be proved tuberculous either bacteriologically or pathologically. The joint symptoms presumably result from "bacillary toxins" produced by the original focus.[1746] Tuberculin treatment was recommended. An abnormal immune response of the host to tubercle bacilli was postulated as cause for the rheumatism, similar to the explanation of joint inflammation of rheumatic fever as resulting from immune response to streptococci [1817] [a theory previously supported by several investigators, but not proved.—Ed.]. One case of tuberculosis of the tonsils and lungs was associated with temporary shoulder pain.[2218] In another instance of arthralgia of only one ankle, no tubercle bacilli were found in the aspirated joint fluid; sodium salicylate was given "with rapid relief." [674] The occurrence of mild arthropathies following the use of old tuberculin in testing for the presence of tuberculosis and even following a flare-up in a pulmonary lesion was reported.[1746] [This is still a vague variety of joint disease. The tuberculosis may be coincidental with rheumatic fever, rheumatoid arthritis or other types of acute or chronic arthritis. There are no convincing data to support the concept of "tuberculous rheumatism."—Ed.]

Syphilitic Arthritis and Synovitis

Syphilitic arthritis and synovitis are uncommon. It was estimated that less than 1 per cent of patients with syphilis have arthritis of syphilitic origin, and not more than 0.1 to 0.5 per cent of diseases of the bones and joints in the United States is due to syphilis.[256]

Clutton's Joints. Hanlon and McLemore [769] reviewed the literature on Clutton's joints and reported two cases occurring in siblings. This syndrome, one manifestation of congenital syphilis in children between the ages of eight and 15 years, was characterized by symmetrical swelling, stiffness and effusion in the knees (85 per cent of reported cases). However, the elbows, ankles, wrists and fingers also have been affected. Pain was usually slight or absent. Interstitial keratitis was often associated. Joint effusion sometimes developed suddenly and, if aspirated, re-accumulated rapidly. Serology of the fluid was usually positive. Roentgenograms of these joints were negative except for swelling of the periarticular tissues with effusion. In three children, a total dose of 50,000 units of penicillin per kilogram of body weight given in seven and one-half days was unsatisfactory.[2234] The response in two other children was poor.[769]

Syphilitic Bursitis. Forty published cases of syphilitic bursitis were reviewed and one case was added.[2049] Only once has bursitis been described in congenital syphilis; most cases occur in the secondary stage, but it may also occur during the tertiary stage. In women the prepatellar bursa was most commonly involved, in men

the olecranon bursa. Occupational trauma appeared important in determining location.

Syphilitic Juxta-Articular Nodes. Nodes resembling the subcutaneous nodules of rheumatic fever and rheumatoid arthritis occurred as multiple painless, hard nodules varying in size from 2 cm. to 1 cm. on the palms of both hands and on the fingers about the joints. The histologic changes in these nodules were considered characteristic of subcutaneous fibroid syphilomas.[1023]

Syphilitic Spondylitis. In two cases of syphilitic spondylitis the characteristic involvement of the cervical spine was again noted.[928] Bence-Jones proteinuria in one of these cases was explained by the associated widespread syphilitic osteitis. [Syphilitic spondylitis must be differentiated from tuberculous spondylitis, pyogenic spondylitis, osteoarthritis and ankylosing spondylitis. The predilection for the cervical vertebrae, the striking radiologic appearance, the positive serology and the symptomatic relief following antisyphilitic therapy are important points in the diagnosis.—Ed.]

Charcot's Joints. This subject will be discussed later under Neuropathic Arthropathy.

Yaws (Frambesia Tropica)

Reports of yaws occurring in the United States are rare; since 1922 only five cases have appeared in the literature. However, in 1948 one case was reported in New York City [1595] and two in Boston.[452] In World War II, 56 cases were reported among the military personnel of the U. S. armed forces.[1895]

Articular and skeletal manifestations may be present during the primary, secondary or tertiary stages of yaws. A complete review of references pertaining to bone lesions was compiled by Hackett.[743] Roentgenologic changes, often asymptomatic, were described.[1971] Nodular periosteal proliferation is characteristic, and osteolytic zones in articular surfaces appear in areas most exposed to trauma. Complete joint destruction may occur. Clinical and radiologic manifestations were similar to those encountered in syphilis. Spirochetes were not demonstrable in the synovial fluid. Although there were no demonstrable neurologic abnormalities, inserting a needle into the femur and tibia did not produce pain. Administration of penicillin was followed by disappearance of joint pains in 12 to 24 hours.[469, 1664] [No details were given as to incidence or type of articular disturbance.—Ed.] Eleven of 17 cases with tertiary bone lesions showed immediate clinical remission of symptoms, and almost complete disappearance of osseous signs within 16 days. Relapse occurred in one of six patients who were followed.[884] In 1,200 early cases in Haiti, repository penicillin (Romansky formula) was effective in more than 94 per cent.[1662]

Meningococcic Arthritis

The concept of infection with the meningococcus is too often limited to that of cerebrospinal meningitis. For clarification, the terms "meningococcus infections" and "meningococcus meningitis" were suggested.[1633]

Incidence of Articular Manifestations. Of 170 patients in military service who had meningococcic meningitis, only nine had arthritis also.[1829] In a civilian series, three of 190 patients had joint involvement.[217] In contrast, arthralgia or arthritis was the most frequent finding, other than fever and rash, in 11 of 16 patients with acute meningococcemia.[2006] Of 17 children with meningococcemia, only two had evanescent arthralgia.[79]

Clinical Data. The most frequent prodromal symptoms are those of an upper respiratory infection,[887, 1633] but severe circumscribed myalgia may be present at onset. Migratory arthralgia and arthritis resembling rheumatic fever are frequent early manifestations,[1633] but acute joint pain and swelling may occur

early.[1829] In patients with meningococcemia, pain in the region of joints may be caused by embolic skin lesions, and the condition is easily confused with rheumatic fever or erythema nodosum.[1829]

In patients with meningitis, mild transitory involvement of multiple joints sometimes appeared first, but the process eventually settled in one or more large joints, most often the knee.[1829] Joint manifestations varied from transitory swelling and arthralgia (often indistinguishable from a toxic reaction to sera or sulfonamides used in treatment) [217] to multiple pyoarthritis.[2044] In an example of the latter, joints containing fluid exhibited no local heat or tenderness, despite the fact that at autopsy these joints were filled with thick creamy pus containing meningococci.[2044]

Laboratory Data. In meningococcemia, the organism may be demonstrated in smears from purpuric skin lesions; in one series, meningococci were found in all cases so examined.[887] In cases with arthritis, the synovial fluid was usually sterile, but at times was frankly purulent and contained meningococci. The organism sometimes was seen on the stained smear of joint fluid when cultures of the same material were negative.[2044] [This occurs not uncommonly in meningococcic arthritis.—Ed.] The demonstration of agglutinins in the serum was of diagnostic value. Five of six patients with negative blood cultures yielded significantly high titers.[79]

Treatment. In cases with meningitis, arthritis was neither prevented nor decreased in incidence in patients receiving sulfonamides or penicillin, nor was the course of the arthritis strikingly altered by these medications. In contrast, 26 patients with meningococcemia were cured rapidly by chemotherapy.[1829] For meningococcic infection, some workers considered sulfadiazine the drug of choice.[79, 1632] Others advocated sulfadiazine plus penicillin.[2044] The prophylactic administration of sulfadiazine to other children in the family was recommended.[79]

While joint fixation should be avoided and active exercises started early, weight bearing should be postponed until inflammation has cleared.[1829] In spite of variations in severity, most patients required four to six weeks of convalescence before joint function was fully restored. Of nine military cases with arthritis, all but one returned to full duty.[1829]

Suppurative Arthritis

Pneumococcal. While primary or "cryptogenic" pneumococcal arthritis occurred in the absence of a discoverable focus,[249, 530, 873] it was usually a complication of pneumonia. One case of pneumococcal arthritis occurred in every 300 cases of pneumococcal pneumonia.[250] Clinical features of pneumococcal arthritis were similar to the other acute pyogenic arthritides, with an affinity for large joints, particularly the knees [250]; symmetrical polyarticular involvement occurred, but rarely were more than two joints involved.

Therapeutic arthrotomy has been generally abandoned. Penicillin, probably more efficacious than sulfonamides, was the treatment of choice.[249, 530] When given systemically, penicillin sterilized the blood before it rendered the joint exudate sterile.[249] Supplementary intra-articular injections of penicillin were used with good results,[2073] but may be unnecessary. In three patients with symmetrical bilateral pneumococcal arthritis who were receiving systemic penicillin, no significant clinical or bacteriologic differences could be demonstrated between joints injected with penicillin and joints not treated in this fashion.[249] The prognosis for complete joint recovery was good if treatment was instituted promptly.

Streptococcal. Suppurative infections in joints due to hemolytic streptococci may occur in infants. In six cases of pyarthrosis in infants under two years of age, two were due to group A hemolytic streptococci.[879] In four of ten infants who had pyogenic arthritis complicating pathologic dislocations of the hip, cultures were positive for hemolytic streptococci.[1474]

Staphylococcal. Staphylococcal infection was the cause of acute purulent arthritis in joints of the hip,[642, 879, 1474] fingers,[1679] knee [708, 804] and shoulder.[879, 2078] Suppurative arthritis may result from wounds that penetrate capsules of the finger joints. Of five cases with this relatively uncommon condition,[1679] in two the responsible organism was a staphylococcus and in three the cultures were negative. An unusual outbreak of staphylococcus infection occurred in one family of seven children; two developed suppurative arthritis, a third acute osteomyelitis, and the same organism was recovered from the nasal mucosae of two of the remaining four children.[804]

Treatment. Additional studies were concerned with the effect of antibiotics on pyogenic arthritis.[642, 708, 890, 1241, 1336, 1474, 1679] In both staphylococcal and streptococcal joint infections in adults and in infants, the combination of intra-articular and systemic administration of penicillin was most effective. Most workers did not support the suggestion [2078] that large intra-articular doses of penicillin alone may be adequate. Early intensive treatment with penicillin for staphylococcal infections was urged to avoid the development of penicillin resistance.[1211]

Several studies reviewed the treatment of suppurative arthritis resulting from war injuries.[244, 281, 764, 1527] In the most comprehensive report, treatment of 184 septic joints in the North Burma area was undertaken at an average of six days after injury and the patients were followed until final discharge. Even though penicillin was not available, amputation was necessary in only one case, and early resection of the joint in three. The importance of complete and early debridement, removal of foreign bodies, and aspiration or drainage of infected articular wounds was stressed.[281] With the use of antibiotics in addition to surgical measures, closure of the articular capsule was recommended uniformly as superior to continuous drainage. In 44 out of 66 gunshot wounds, most of them infected, healing was complete or plastic surgery could be done within five weeks.[244] Intra-articular penicillin combined with systemic penicillin was found to reduce the duration of convalescence.[1527]

Typhoid Arthritis

Arthritis is a rare complication of typhoid fever. Skeletal infections caused by *Salmonella typhosa* occur in about 1 per cent of those infected with this organism.[1981] Spinal inflammation is usually confined to the vertebral periosteum. The diagnosis may be suspected in patients with backache, localized tenderness and restricted motion during or following typhoid fever. In an unusual case, paraplegia due to compression of the spinal cord by a subperiosteal typhoid abscess developed after one month of fever. Although roentgenograms were negative, material obtained by lumbar puncture yielded a pure culture of *S. typhosa*.[18]

Other Salmonella, alone [2095] or in combination with *S. typhosa*,[678] were cultured from fluid aspirated from the knees of infants with arthritis. One patient with mixed infection responded well to streptomycin.[678] Such infections must be rare, as in 2,949 cultures of Salmonella from human material, there were only five instances in which these organisms were recovered from joints.[487]

[Bacteriologists have recently placed the typhoid bacillus in the genus Salmonella. Clinically, the disease caused by the typhoid bacillus is known as typhoid, but the bacteriologists commonly speak of this condition as Salmonella fever. Infections in man due to Salmonella are common, and errors in mistaking other Salmonella organisms for typhoid bacilli can be eliminated in the United States by utilizing the recently established Salmonella typing centers.—Ed.]

Brucellosis

Incidence and General Clinical Data. Concern was expressed by many authors at the increasing incidence of brucellosis in both man and domestic animals.[401, 517, 1898, 2255] It was ranked as the most prevalent disease of animals transmitted to man,[1281] the incidence being closely dependent on the size and importance of the dairy and food-animal industries.[492] In Minnesota, at least 60 per cent of proved cases were occupational in origin. Direct contact with infected animals and tissues was more important than the ingestion of raw milk.[1281]

Spink[1898] summarized studies on the pathogenesis of human brucellosis, stressing the important concepts of intracellular parasitism resulting from invasion of tissues, and the rôle of hypersensitivity to Brucella antigens in the clinical manifestations of the disease.

The extremely diversified clinical picture was again emphasized.[131, 332, 401, 491, 754, 1242, 1742, 1789] The most frequent symptoms were fatigue, muscle and joint aches and pains, nonmigrainous headache, digestive complaints and low grade fever. In chronic brucellosis the symptoms were often multiple, vague and difficult to evaluate.[388, 1242] The majority gave no history of an acute phase or exacerbations.[491] Important complications were salpingitis, cystitis and pyelitis,[791] ocular, pulmonary and skin manifestations.[1742] Glandular swellings in some cases simulated Hodgkin's disease.[1018] Symptoms sometimes suggested a diagnosis of rheumatic fever or infectious hepatitis, and brucellosis was responsible for pneumonitis in four of 21 patients.[870]

Symptoms Referable to Joints and Muscles. Arthralgia involving any or all joints was a common symptom.[870, 1988] Arthralgia and myalgia were described in 100 per cent of 74 patients,[1441] and in 65 per cent of 74 patients.[388] In 141 children with "possible brucellosis," 50 had vague pains, chiefly in the legs and back.[1742] Generalized aching in the lumbar spine and long bones was a feature of the acute phase.[1244] Severe pain radiating down one or both sciatic nerves was a frequent complication of melitensis infection.[1899]

Localized Bone and Joint Involvement. Brucellosis was found to have no etiologic or contributory importance in rheumatoid arthritis, ankylosing spondylitis or osteoarthritis, but a possible relationship to atypical rheumatoid arthritis.[888] No cases of chronic arthritis attributable to brucellosis were found in other series.[1898] In contrast, Harris considered arthritis a common but rarely considered manifestation. Of 427 patients with brucellosis, 17.3 per cent were considered to have atrophic or hypertrophic arthritis related to their infection.[791]

Osseous lesions other than chronic arthritis are fairly frequent and tend to involve the vertebrae, pelvis and long bones. Such involvement was considered an osteomyelitis, and characteristic granulomata were described in such lesions in both man and animal.[1243] Osteolytic lesions of the spine may induce the symptom-complex of a herniated disc or spondylitis.[1898, 1936] Vertebral osteomyelitis was most common in the convalescent phase.[768] Gross destructive lesions and epidural abscess occurred in and around the lumbar vertebrae.[491, 870, 1988] Infectious arthritis of the hip was observed,[208] and infected emboli produced osteomyelitis in the shafts of long bones.[1244] Chronic osteomyelitis without drainage and producing little disability should suggest

brucellosis.[1244] Bone production is the main feature distinguishing this from Pott's disease.[768]

[There is general agreement that arthralgia and myalgia are very common in active brucellosis, and that Brucella occasionally cause localized bone and joint infection, especially in the spine and hips. There is sharp disagreement with respect to the rôle of brucellosis in the pathogenesis of chronic arthritis, i.e., rheumatoid arthritis and spondylitis, and osteoarthritis. It is obvious that this disagreement stems from varying criteria for the diagnosis of brucellosis. Workers requiring strict bacteriologic proof report no cases of chronic arthritis; those whose "evaluation was made on the basis of clinical study and response to vaccine therapy" [791] report a significant incidence of chronic arthritis.—Ed.]

Diagnosis. This remains in a confused state. Diagnostic enthusiasm coupled with uncritical reliance on laboratory data has led not only to many wrong diagnoses but also to defective clinical concepts of the disease. The great variability in the course and symptomatology, together with a dearth of distinguishing clinical features, has led to reliance on laboratory tests which are meaningless when considered apart from the patient.[492, 1342]

The diagnosis is established with certainty only by positive cultures.[401, 492, 754, 776, 1342] The secrets of success were early and persistent attempts to obtain such cultures,[492] but even with meticulous procedure, isolation was accomplished in less than 25 per cent of active cases.[1900] The guinea pig was the most satisfactory animal for inoculation tests for Brucella.[776] The organism was recovered from sternal marrow and lymph nodes,[1342] spinal fluid [1281] and exudates of soft tissue and joint abscesses.[208, 870] These may be positive when venous blood is sterile.[492]

A positive agglutination test was considered next in importance,[492, 790, 1013] but the test was negative in most "chronic cases." [791, 1244] Opinions varied on significance of titer strength,[131, 1244] and a changing titer was thought to be more significant than an arbitrary "diagnostic" level.[179, 776, 1342] Others considered the test of little value [1441, 2255]; the results varied greatly from one laboratory to another [197, 492, 722, 1342] and at times were not specific.[1898] Symptom-free persons may give a positive agglutination within the diagnostic range.[777] Reports on the value of skin tests were again conflicting. Most workers considered it of little value and indicative only of recent or past infection.[197, 388, 401, 491, 1013, 1342, 2255] Others considered it reliable.[131, 791, 1441] The interpretation should be analogous to that of the tuberculin test.[492, 1898] The opsonocytophagic test was considered dangerous and technically difficult.[197, 492, 1342] Leukocyte counts were slightly low or normal, with frequent lymphocytosis.[784]

Treatment. With the development of the newer antibiotics, definite progress was made in treatment, but no method is regularly successful in eradicating Brucella from all patients.[492, 1898]

It was generally conceded that sulfonamides alone and streptomycin alone are relatively unsatisfactory.[492, 870, 1900] Sulfonamides in conjunction with blood transfusions were occasionally effective.[1712] The demonstration that combined sulfadiazine and streptomycin therapy is superior to other methods in eradicating *Br. abortus* from infected chick embryos suggested the first "specific therapy." [1813] Clinical results of this combined therapy "surpassed any form of therapy we have encountered in the past 10 years" (Spink [1900]) and was followed by few relapses.[208, 492, 871] However, aureomycin subsequently was found to be more practical and more effective, especially in abortus and melitensis infections.[208, 410, 618, 1899] Herrell and co-workers [870, 871] subsequently reported 35 patients treated

with combined aureomycin and dihydrostreptomycin, with only one subsequent symptomatic relapse and no bacteriologic relapses. The effectiveness of this combination was supported by experimental observations in mice.[835] Encouraging preliminary observations were also reported with the use of chloromycetin.[2112] Eisele [492] emphasized the need for further experience, particularly with respect to relapse rates, before drawing conclusions regarding the effectiveness of aureomycin and chloromycetin.

Rat Bite Fever (Haverhill Fever; Sodoku)

Two distinct diseases have come to be known as "rat bite fever," the infecting agents of which are entirely unrelated: *Spirillum minus* (sodoku) and *Streptobacillus moniliformis* (Haverhill fever).[952, 1234] The spirillary form was the common variety; infection with the streptobacillus was much rarer.[1234] Both infections can be transmitted from rats but also by the bite of a dog, cat or other carnivore.[952] It was estimated that about 3 per cent of the rats in Japan are infected. In Vancouver, Canada, 14 per cent of 150 rats were infected with *Spirillum minus*.[952]

Haverhill Fever. The streptobacillary form was usually characterized by a short (three to five days) incubation period, fever, migrating polyarthritis, rash, and a relapsing course. Since 1926, when Haverhill fever (erythema arthriticum epidemicum) was first described, a total of 46 sporadic cases has been reported in the United States.[1482] The diagnosis is made by finding the organisms in body fluids or by demonstrating an agglutination titer of 1:80 or higher.[1602] *Streptobacillus moniliformis* bacteremia may occur with only minor clinical manifestations.[1203] Though it is commonly transmitted by a rat bite, ingestion of contaminated food resulted in this infection.[1909] Positive blood,[1203, 1437, 2132] urine and stool cultures [1161] were obtained using media enriched with ascitic fluid or serum.

Until the advent of penicillin the disease frequently ran a protracted and serious course.[28, 1094, 1161, 1234] Penicillin usually was effective,[1094, 1161, 1234] though one patient, unimproved on penicillin, improved rapidly on streptomycin therapy.[1909] One patient with Haverhill fever had a protracted course (19 months), failed to respond to sulfadiazine, penicillin and streptomycin, and died from the disease.[1437]

Sodoku. The spirillary disease was characterized by an incubation period of seven days or more,[1234] by chills and relapsing fever, development of a chancre-like lesion at the inoculation site, regional adenopathy, purplish maculopapular rash, leukocytosis, and a false positive serologic test for syphilis in 50 per cent of cases.[2132] The organism may be identified by direct dark field examination of the blood [1592] or lymph from the primary lesion, though most commonly mouse inoculation was employed.

The newer arsenical drugs were very effective against *Spirillum minus;* neoarsphenamine and oxophenarsine hydrochloride both gave satisfactory results.[1203] Streptomycin therapy resulted in prompt clinical response in a nine year old girl.[988] Successful treatment with penicillin was also reported.[1592, 1669, 2132]

Rarer Forms of Specific Infectious Arthritis

Variola (Smallpox). Chatterjee [303] reviewed 2,341 cases of smallpox during the 1948 epidemic in Calcutta; a total of 10 patients (0.43 per cent) developed arthritis, most of them children. The elbow was most often involved, frequently bilaterally. Joint symptoms began three to four weeks after the onset of the disease, frequently after the skin eruptions had cleared and the scales had begun

to fall off. The joints were swollen, painful when moved, and the limitation of motion frequently persisted for several weeks. Roentgenograms revealed the head of the radius most often affected, with destruction of the epiphysis and subperiosteal bone formation, without cartilage destruction. The clinical course of one illustrative case was reported in which the arthritis completely disappeared following treatment with sulfadiazine and penicillin.

"Dysenteric Arthritis." Among 173 patients in the Mediterranean Theater with proved or probable bacillary dysentery, 20 (11.6 per cent) had arthritis manifested by severe and protracted synovitis which did not respond to sulfonamides.[1829] Pyarthrosis of the knee due to *Salmonella suipestifer* was successfully treated with streptomycin; clinical improvement was evident three days after therapy was begun, and the joint cultures became negative.[675] A similar patient was given a combination of penicillin and sulfadiazine with good results.[792] [Other reports of postdysenteric arthritis are discussed under Reiter's syndrome.—Ed.]

Granuloma Inguinale and Lymphopathia Venereum. In spite of certain resemblances and their confusing names, these are two definitely separate disease entities.

Granuloma Inguinale; Granuloma Venereum. The causal agent is a coccobacillus, *Donovania granulomatis* (Anderson). It was believed by most authors not to be a venereal disease but probably transmitted by *Phthirius pubis.*[259] The primary lesion was usually located in or around genitalia. The incidence of extragenital lesions was 4.5 to 6 per cent.[1521] These usually occurred by contact, but vascular dissemination to the osseous system has been reported.[1263, 1521, 1670] In a fatal case of disseminated granuloma inguinale with miliary involvement of bones and joints, many symmetrical large joints and all the small joints of hands and some of the feet were swollen and fluctuant; some lesions ulcerated through the skin. "Donovan bodies" were seen in the involved tissue.[1263] The roentgenographic features of cases with bone involvement were described.[1521, 1670] This was a disease of increasing frequency,[1263] and low contagiousness,[709] which affected for the most part poor and unclean people.[709]

Lymphogranuloma Inguinale; Lymphogranuloma Venereum; Lymphopathia Venereum. This is a venereal disease of worldwide distribution.[1128, 1772] Its causative agent, a filterable virus related to the psittacosis group, was isolated from the blood of a human for the first time by Wall.[2109] Though the most common and characteristic localization of the disease process is the inguinal lymph nodes, it is a widespread systemic disease.[1772] Constitutional symptoms frequently accompany its acute manifestations. Skin reactions of the erythema group and joint symptoms are common during this stage: arthralgias,[1529, 1604, 2139] polyarthritides of migratory nature,[2146] arthritis,[2139] joint effusions in severe cases.[1604] The acute arthritis may resemble acute gonorrheal infection.[1178] This disease can be suspected in children when, in addition to vague rectal or genitourinary symptoms and adenitis, "unexplained joint pains" or erythema nodosum are present.[2146] Joint effusions appeared in some patients during sulfathiazole treatment, and all recovered when the drug was discontinued.[2072] Koteen [1128] classified the joint and bone involvement as lesions from which the virus has not been recovered, but considered the supporting evidence adequate to regard them as part of the clinical manifestations of the disease. He observed joint involvement during the first weeks of the disease and was impressed by the rapidity with which it responded to therapy. "Ten per cent of most chronic cases suffer with arthritis, which often is severe enough to confine the patient to bed." [2139] [No details are given.—Ed.]

Several papers dealt with a new reagent (Lygranum) for the Frei test and the complement-fixation reaction.[1814]

Sulfathiazole seemed to be the best therapeutic agent in 1947.[877] [This report was published before the newer antibiotics with virucidal properties became available.—Ed.] The response to aureomycin in 25 patients with lymphogranuloma venereum was described as gratifying.[2227, 2228] [There was no reference to joint symptoms.—Ed.]

Miscellaneous. Other unusual types of infectious arthritis were reported. Morgan and Comroe[1429] reviewed a number of diseases occurring in the tropics with more or less prominent articular manifestations. Polyarthritis of the tarsal joints was associated with a case of epidemic poliomyelitis.[1591] *Proteus vulgaris* infection of both sternoclavicular joints secondary to infection of the umbilicus occurred in a 10 day old infant. Such cases are rare and usually fatal; this child was successfully treated with sulfadiazine.[167] Osteitis pubis and suppurative arthritis of the hip due to Pseudomonas developed in one patient eight months after suprapubic prostatectomy.[604] Pyarthrosis of the knees caused by *Bacillus pyocyaneus* (*Pseudomonas aeruginosa*) responded to streptomycin therapy.[280]

Mycotic Diseases of Joints

Coccidioidomycosis; Coccidioidal Arthritis. This mycotic infection was endemic in southwestern United States, including the great central valley of California, the western slope of the Coastal Range, all of Arizona and New Mexico, southern Utah and Nevada, western Texas and northern Mexico. It was estimated to have occurred in approximately 6,000 soldiers who trained in this area during the late war.[570]

Three stages of the disease were recognized: (1) primary, (2) persistent or intermediate, and (3) progressive or disseminated.[461, 1413] The primary stage was clinically manifest in about 25 per cent of cases and was characterized by respiratory symptoms.[1413, 1864] Occasionally erythema nodosum or erythema multiforme was a striking feature.[1864] Articular involvement was not infrequent,[1413] at times closely simulating rheumatic fever, and usually subsiding within one month without residual deformity.[1413, 2007] The majority of cases were symptomless, a positive coccidioidin skin test being the only evidence of present or past infection.[825]

In the intermediate stage the symptoms and pathologic changes were with few exceptions strikingly like those of tuberculosis. Pulmonary lesions characterized this stage.[461]

In about 0.25 per cent of individuals with primary infection, the disease became progressively and widely disseminated, involved many different tissues, and resulted in 40 per cent mortality.[570, 1864] The involvement of bone constituted one of the most characteristic features of this stage. Miller and Birsner[1399] collected 17 cases of coccidioidal granuloma of bone. The roentgen findings were principally osteolytic; occasionally there was some sclerosis and, in some, linear calcifications in the soft tissue adjacent to bone. The roentgen appearance closely resembled tuberculosis.[1758] Joints were not frequently the site of the granulomatous process, but sometimes were involved by direct extension of a focus in adjacent bone. Lesions in the knee, elbow, ankle, sternoclavicular and sacroiliac articulations were described.[570, 2007]

Dust control was a difficult but effective prophylactic measure.[1863] There was no curative treatment for the disease. Rest, salicylates and convalescent serum have been advocated for the primary stage.[254] Excision of the involved part was feasible in some cases with granulomatous bone involvement.[681, 1758] The lesions did not respond to penicillin or streptomycin.[254, 461, 813, 1146] The outlook in the progressive form of the disease was still regarded as hopeless.[461]

Histoplasmosis. It is now well established that histoplasmosis is neither a rare nor always a fatal disease.[281] A complement fixation test for histoplasmosis was described.[615] The generalized form of histoplasmosis is characterized by fever, weight loss, anemia, leukopenia and enlargement of the liver and spleen. In one patient, arthritis developed in a wrist, elbow, shoulder and ankle, with skin lesions resembling erythema nodosum.[834] Osteolytic skeletal lesions and fluid in the knee joint were observed in another case.[316] [The articular tissues in this fatal case were not examined post mortem.—Ed.]

The Adrenal Cortex and Rheumatic Diseases

The remarkable clinical effectiveness of cortisone and corticotropin in many of the rheumatic diseases promptly led to attempts to link their pathogenesis with the function of endocrine glands, especially of the adrenal cortex. It soon became apparent that these hormones could influence the course of a host of non-rheumatic diseases. At the same time, knowledge of endocrine physiology was expanding rapidly. Numerous articles attempted to keep the medical profession informed of the results of fundamental as well as clinical investigation and the changing concepts which each new development seemed to require.[176, 890, 894, 957, 1062, 1765, 1905, 1906, 2055, 2057, 2100] [It is manifestly impossible to review the voluminous literature on these subjects. This section deals with contributions having a direct bearing on those aspects that the rheumatic diseases have in common. Additional work bearing on the individual diseases will be found in the appropriate sections. —Ed.]

Pituitary-Adrenal Physiology. Starting from the simple fact that one of the anterior pituitary hormones, corticotropin or ACTH, controls the release of hormones from the adrenal cortex, the outlines of a highly complicated and sensitive self-regulating mechanism endowing the higher organism with relative freedom from a constantly changing environment have become gradually apparent.[1765] A most striking feature of the pituitary adrenocortical system is its ability to endow the organism with resistance, not to a few but to all types of stress.[1765, 1804, 1807] The regulation by the hypothalamus of the release of ACTH from the anterior pituitary through humoral and neural mechanisms[948] and an interrelationship to the autonomic nervous system through epinephrine[1344, 1345, 1650] have been demonstrated. In addition to autonomic release of corticotropin, its output is regulated by a metabolic mechanism whereby low levels of circulating adrenocortical steroids stimulate and high levels inhibit the release of corticotropin.[1345, 1765, 2055] Low levels of circulating adrenocortical steroids were assumed to result from their increased utilization in peripheral tissues.[1765, 2055]

While the ACTH used in virtually all studies reviewed was a protein, with a molecular weight of about 20,000, isolated from animal pituitary glands, Li[1216] has prepared from a peptic digest of this protein a peptide mixture which possesses adrenal-stimulating activity. ACTH in body fluids was determined by bio-assay[190]; following intravenous injection it disappeared rapidly from the plasma, reaching control levels two hours after the infusion was terminated.[1766] By intramuscular injection, the usual route of administration, maximum duration of action was about six hours.

The immediate metabolic effects following ACTH administration are due to release of adrenocortical steroids, and in general are similar to those seen after cortisone. It has been convenient to divide the over-all effects on a wide variety

of metabolic processes influenced in man into three general groups: (1)electrolyte-regulating effect; (2) regulation of utilization of organic substances, especially carbohydrate, protein and fat; and (3) androgenic and anabolic effects.[2055] The variety of metabolic effects and the isolation of 28 structurally different steroids from adrenal tissue at first led to the assumption that several steroids were produced. The most potent electrolyte-regulating steroid was synthetic 11-desoxycorticosterone (DCA), while the most active "carbohydrate-regulating" steroids, cortisone (compound E) and compound F (recently dubbed "hydrocortisone") exerted a relatively weak sodium-retaining effect. Compounds A and B (corticosterone) were intermediate in both effects.[2055] Further experience indicated that cortisone and compound F [581] produced changes in electrolyte and organic metabolism similar to those induced by ACTH. Even androgenic effects were observed during cortisone administration [1905, 1906]; it was suggested that androgens may arise from degradation of cortical hormones.[1765] [While the exact nature of the secretion of the adrenal cortex is unknown, there is currently wide acceptance of evidence that compound F is the chief steroid released by ACTH [1906]; perfusion experiments with isolated adrenal glands indicate that various species produce predominantly compounds B and F. Other steroids found in adrenal tissue are regarded as intermediates in biosynthesis or degradation.—Ed.]

The effect of adrenal stimulation or of adrenal steroids on electrolytes is characterized by retention of sodium and chloride, increased excretion of potassium, and increased plasma and extracellular fluid volume [2055]; they also decrease the concentration of sodium and chloride in thermal sweat.[328] Since there is no direct means of measuring the steroid responsible for electrolyte regulation, this activity is estimated indirectly by alterations in renal excretion of electrolytes, in mineral composition of sweat, and by changes in hematocrit or body weight.

The effects of these substances on intermediary organic metabolism were summarized as: (1) an increase in blood glucose level and in liver glycogen stores; (2) increased conversion of protein to carbohydrate; (3) increased mobilization and utilization of depot fat; (4) increased urinary excretion of uric acid, attributed usually to increased renal clearance, and (5) lysis of fixed lymphoid tissue and a transitory decrease in circulating lymphocytes, with a more lasting and almost complete disappearance of circulating eosinophils during the period of hormone action.[2055] The production of temporary diabetes mellitus in normal humans by ACTH was studied intensively by Conn and co-workers,[339, 340] who found it not always associated with a negative nitrogen balance, and correlated its occurrence with alterations in uric acid metabolism and with decreases in blood glutathione. An approximate measure of this division of corticosteroid activity was obtained directly by following urinary excretion of 11-oxysteroids [also termed glucocorticoids, formaldehydogenic steroids, neutral reducing lipids, or "cortin-like substances," according to the methods of determination, all admittedly cumbersome and only approximate—Ed.], or indirectly by measuring the fall in circulating eosinophils or change in the ratio of uric acid to creatinine in the urine.[2055, 2092]

The adrenal androgenic and anabolic effects were assumed to be masculinization, and retention of nitrogen, phosphorus, potassium, sodium and chloride, similar to the effect of testicular androgens. The excretory products of androgenic steroids, the urinary 17-ketosteroids, were often measured as an index of this phase of adrenocortical function; in the female, nearly all androgenic effects are derived from adrenocortical androgens, whereas in the male the adrenal androgens appear to account for about two thirds of the androgenic substances, the remainder being derived from the testes.[2088]

These various measurements were employed as indices of the functional state of the adrenal cortex, particularly in combination with ACTH stimulation.[1603, 2057] The usefulness and limitations of epinephrine in testing the responsiveness of the hypothalamic-pituitary-adrenocortical mechanism were presented [1650] and its limitations emphasized.[1765] [More recently, considerable doubt has been raised concerning the validity of the correlation between the eosinophil response to epinephrine and concomitant release of corticosteroids by the adrenal.—Ed.] Sometimes overlooked in the interpretation of such studies was the fact that "the cortical hormone plays a general supportive rather than an initiating rôle in body processes," and that its actions "are determined in no small measure by the functional status of the tissue cells themselves." [1765] ACTH was found to produce a more prompt and greater rise in urinary excretion of corticoids than of 17-ketosteroids,[1910, 2092] and evidence was obtained that a small percentage of administered cortisone is excreted in the urine as 17-ketosteroids and corticosteroids.[1906] If the urinary 17-ketosteroid excretion was initially in the normal range, it decreased promptly when administration of cortisone was begun, and at times remained at low levels long after the hormone was stopped, pointing to depression of at least some functions of the adrenal cortices by cortisone.[1905, 1906]

Extensive changes which occur in structure of cells, tissues and organs following adrenal stimulation or administration of adrenocortical steroids were summarized in the reviews of Sayers [1765] and Ingle.[957] An important difference between ACTH and cortisone is the anatomic and functional state of the adrenal cortex during and following their administration.[2057] In contrast to the hypertrophied adrenals following ACTH, cortisone induces adrenal atrophy in experimental animals [44, 2194] and in man.[1905] There is associated evidence of decreased adrenocortical function during and following cortisone, an effect attributed to suppression by cortisone of endogenous corticotropin production by the anterior pituitary. Cytologic changes in the anterior hypophysis, "comparable to those described by Crooke in the hypophyseal basophile in Cushing's disease and related conditions," were found after cortisone and ACTH treatment.[659, 1174] [There is need for further information on structural or functional changes induced by ACTH or cortisone in the pituitary and related hypothalamic centers.—Ed.]

The effects of cortisone and ACTH on other endocrine systems must be considered in interpreting the over-all effects of these hormones. Evidences of depression of thyroid function, as measured by the uptake of radioactive iodine and the level of serum protein bound iodine,[779, 886] were recorded; changes in the basal metabolic rate were the resultant of such depression plus the antagonistic calorigenic action of adrenocortical steroids.[886] There was fragmentary evidence of an effect of ACTH and cortisone on the posterior pituitary, on pancreatic islet cells, and on gonadal function.[2057]

Adrenocortical Function in Rheumatic Diseases. Indices of adrenocortical function were studied almost exclusively in patients with rheumatoid arthritis. Variable results were reported from studies of urinary 17-ketosteroid excretion. Levels were found to be essentially normal in 11 patients with peripheral rheumatoid arthritis, but to be elevated in 35 patients with rheumatoid spondylitis.[404] Other workers failed to find elevated values in eight patients with rheumatoid spondylitis, and found values in the normal range in 76 per cent of 67 patients with rheumatoid arthritis.[422] Similar results were reported by Hench, Kendall, Slocumb and Polley,[854] who found values below the normal

range in only 29 per cent of an unspecified number of patients. Others reported mean values in groups of patients with rheumatoid arthritis to be about one-half of those obtained in groups of normal subjects.[595, 937]

Relatively few determinations of urinary corticoid excretion were reported. Howard, Venning and Fisk [937] found subnormal levels by bio-assay in all of nine patients with rheumatoid arthritis; in six of these, corticoids were also determined by a chemical method and found to be low. In contrast, values in the normal range were found in 15 men [1921] and in an unspecified number of patients [854] with rheumatoid arthritis. [Factors such as age, level of physical activity, and the nonspecific effect of chronic disease, as well as sex, affect the level of 17-ketosteroid excretion and may influence corticoid excretion levels. Much more information regarding factors influencing the "normal" range, and the nonspecific effect of debilitating illness, must be available before the significance of such determinations can be evaluated.—Ed.]

Thorn and Bayles [2055] obtained a normal eosinophil response to ACTH in nine of 10 patients with rheumatoid arthritis, which seemed to suggest that the available reserve of the adrenal cortex was not noticeably impaired. The average eosinopenia following epinephrine was slightly lower in 14 patients with rheumatoid arthritis than in normal subjects.

Rheumatic Diseases as "Diseases of Adaptation." Selye has described the pattern of alterations which may occur upon exposure of an animal to stress under the term "general adaptation syndrome"; he divides this syndrome into three stages, the alarm reaction, the stage of resistance and the stage of exhaustion. During these last two stages, observations were made which were "most readily compatible with the view that during the general adaptation syndrome, certain hormones of the anterior pituitary and adrenal cortex are produced in excessive amounts in order to increase adaptation to stress, but the resulting endogenous hormone overdosage may become the cause of certain cardiovascular, renal and joint diseases. Thus developed the concept that many of the most common maladies of man are 'diseases of adaptation,' that is to say, the by-products of normal adaptation to stress" (Selye [1804]). The similarity between pathologic changes produced in experimental animals by treatment with DCA, usually with unilateral nephrectomy and a high salt intake as necessary adjuncts, to those seen in certain disorders in man (including rheumatic fever, rheumatoid arthritis and periarteritis nodosa) has been the chief experimental evidence for this concept.[1804, 1805, 1807] Comparable lesions have been produced by administering a lyophilized extract of anterior pituitary tissue [but not by ACTH—Ed.]

[It is not justifiable to conclude that morphologic similarities between experimental lesions and those in human disease indicate that they are the same disease, or even attributable to the same etiology.—Ed.]

Experimental arthritis and cardiovascular lesions produced in rats by overdosage with DCA in combination with "sensitizing" factors were noted previously (Ninth Rheumatism Review). Subsequently, Selye [1806] commented about lesions produced by this method: "Curiously, arthritis occurred in only a small percentage of our experimental animals, although other 'rheumatic' changes (e.g., a 'rheumatic' type of arteritis, myocarditis and encephalitis) were constantly present. Furthermore, even when an arthritis developed during the first weeks of treatment, it tended to disappear in spite of continued DCA administration; only rarely did such lesions progress toward what might be called an experimental replica of rheumatoid arthritis." In a

carefully designed study, Harrison [805] was unable to induce joint disease by DCA administration in rats, despite various "sensitizing" procedures. Animals dying of pneumonia, and after exposure to cold, developed cardiac and renal lesions whether treated with DCA or not; the pathology was actually less severe in the DCA-treated rats. Pemberton and associates [1550] were also unable to confirm Selye's observations. Articular lesions occurred in both untreated and DCA-treated rats, but were characterized by focal areas of degeneration and ulceration of the articular cartilages. Such lesions were most frequent in rats on an unbalanced diet, or those receiving DCA. The incidence and severity of lesions were not altered by exposure to cold, unilateral nephrectomy, adrenalectomy, thyroidectomy or gonadectomy. [Unfortunately, both Harrison and Pemberton et al. employed a relatively small number of animals in their studies.—Ed.]

More recently, Selye [1806] has reported antagonistic effects of cortisone and DCA on "arthritis and periarthritis" induced in ankle joints of rats by the injection of dilute formaldehyde solutions beneath the plantar aponeurosis of the paw. The immediate edematous and hyperemic reaction following this procedure (in adrenalectomized animals on a high salt intake) persisted longer in DCA-treated animals, and subsided more rapidly when cortisone was administered, either with or without DCA. In intact rats, treatment with ACTH diminished the immediate reaction to the irritant; pretreatment with ACTH greatly diminished the changes persisting after two to four weeks, while lyophilized anterior pituitary extract increased them slightly. In animals exposed to a variety of "stresses" for 24 hours before injection of the irritant, the immediate reaction was almost completely suppressed.[1806] The same technic was used to evaluate the influence of combined DCA and ascorbic acid, a combination which appeared to protect normal and adrenalectomized rats against formaldehyde-induced "arthritis." [237] [While Selye describes a chronic persistent periarthritic and arthritic reaction induced by repeated injections of formaldehyde, the reported effect of hormones is based on changes in immediate inflammatory reactions during a period of a few days to a few weeks. In describing this lesion, Selye states: "Microscopically, in the acute edematous stage, it resembled the rheumatic, in the chronic stage, the rheumatoid type of arthritis." We have been unable to find any description of histologic findings which would permit independent judgment as to whether these lesions are analogous to any type of arthritis in the human. Until convincing histologic evidence to the contrary is submitted, it seems justifiable to regard these observations as another example of the ability of cortisone to suppress and of DCA to aggravate inflammation in a nonspecific manner, without implications as to the pathogenesis of joint disease. To label any inflammation in an extremity "arthritis" has as little meaning in experimental medicine as it has in clinical medicine.—Ed.]

A critical analysis of Selye's hypotheses from the viewpoint of an endocrine physiologist [1765] was particularly valuable: "Interpretations of the phenomena, although skillfully threaded together into an attractive and comprehensive concept, are open to considerable criticism." Specific criticisms included failure to consider increased tissue needs in evaluating "excessive" production of adrenocortical steroids; the difficulty of uniformly reproducing pathologic lesions in experimental animals by DCA administration; the failure to induce such lesions by overdosage of adrenal cortical extract, cortisone or compound F; the possibility that results obtained with lyophilized anterior pituitary powder were due to toxicity or bacterial contamination of the preparation; and lack of convincing evidence that chronic exposure of animals to stress (uncomplicated by DCA administration) induces pathologic changes characteristic of the collagen diseases in man.

[The discovery of the widespread clinical effectiveness of ACTH and cortisone (incidentally, made quite independently of Selye's hypothesis) served to focus interest

on the concept of "diseases of adaptation." At the same time, it required modification of the hypothesis. No longer could simple overproduction of adrenal steroids be responsible for diseases which were ameliorated by their administration; an imbalance of adrenal secretion was postulated, with excessive production of "mineralocorticoids" (electrolyte regulating) in relationship to "glucocorticoids" (11,17-oxysteroids). One of us, W. D. R., has applied Conn's [238] method of determining the electrolytes in sweat to this problem; no evidence of excessive electrolyte-regulating activity was obtained in patients with rheumatoid arthritis. As evidences of electrolyte-regulating properties of cortisone and compound F have accumulated, there has been a definite tendency to move the site of the postulated hormonal imbalance upstairs to the pituitary level. There can be little question that Selye has developed a unified concept of a fundamental biologic mechanism in his descriptions of the alarm reaction and the general adaptation syndrome. It will require generations to determine to what extent, if any, this concept is concerned in the pathogenesis of disease; a proved relationship has as yet not been established for any disease. In the meantime, it is important for Selye's audience to appreciate that he regards his hypothesis, not as an established fact, but as "a preliminary map—albeit largely incomplete and partly inaccurate—needed *now* by those eager to exploit this field." [1907] Pickering [1569] aptly cautioned: "The history of medicine shows how great is the tendency for a tentative and imperfectly documented hypothesis to assume the guise of a so-called fundamental principle. This tendency is particularly great in the diseases here considered, whose causation has hitherto been shrouded in impenetrable darkness, now at last dimly lit."—Ed.]

Mode of Action of Cortisone and ACTH in Rheumatic Diseases. The search for the mechanism by which these hormones produce their dramatic suppression of rheumatic diseases has taken many directions. Their use in rheumatoid arthritis was originally suggested by the observed potentiality of natural remissions in the disease, particularly in association with pregnancy and jaundice.[848] Subsequent investigations have neither established nor disproved that adrenocortical hormones are the common denominator in spontaneous remissions. While there is some evidence of increased adrenocortical activity during the last trimester of pregnancy,[976] no claim has been made that this explains remissions occurring with pregnancy; there is even less factual information concerning the hormonal status during jaundice. The adrenal physiologist was "at a loss to give a rational explanation to these empirical discoveries" (Sayers [1765]).

Inhibition of Hyaluronidase Action. Using a carefully standardized method, Opsahl [1809, 1810, 1811] demonstrated that the spreading effect of testicular hyaluronidase in the skin of experimental animals was enhanced by adrenalectomy and inhibited by adrenal cortical extract, cortisone and, to a lesser extent, by compound A. Either systemic administration or local application of these steroids was effective. Such an immediate inhibitory effect was confirmed,[2193] and similar inhibition of hyaluronidase activity in the skin of humans was reported to follow epinephrine stimulation.[1837] In contrast, after four months of local applications of adrenal cortical extract, skin in the treated area showed an accentuation of the slow phase of spread with hyaluronidase.[824] [Some conflicting results in such studies may be due to controllable sources of error in methods.[822]—Ed.] The permeability of membranes (chiefly from the excised bladders of rabbits) [1798] and of synovial membrane (as reflected by the urinary excretion of intra-articularly injected phenolsulfonphthalein) [1799] appeared to be increased by DCA and hyaluronidase; the effect of hyaluronidase appeared to be antagonized by cortisone and several other steroids.

[Several studies,[125, 1509, 1510] including some reported since the period covered by this review, have shown unequivocally that adrenal cortical extract, as well as ACTH and corti-

sone, does not alter the permeability of the normal joint membrane or any other tissue that has been tested. However, when permeability has been increased by hyaluronidase administration or by inflammation, then the 11-oxysteroids and ACTH tend to reduce the permeability toward normal. The possibility that a reduction in permeability is an important common denominator in the anti-inflammatory action exercised by cortisone and ACTH has been emphasized recently by several writers.—Ed.]

Another approach implicating hyaluronidase has been the demonstration of a decrease in the nonspecific hyaluronidase inhibitor in serum of patients treated with ACTH and cortisone,[9, 523] discussed more fully under the sections on Rheumatic Fever and The Basic Structure of Connective Tissue.

Inhibition of Hypersensitivity Phenomena. Both clinical [278, 810, 986] and experimental hypersensitivity are suppressed by ACTH and cortisone. Detailed study of factors involved in immune reactions indicated that these hormones usually did not alter circulating antibody levels,[548] elicit an anamnestic response,[547, 548] or stimulate antibody release.[762, 793] Cortisone induced a fall in complement titer of guinea pigs.[1842] Tuberculin sensitivity was depressed by cortisone in animals [793] and by both ACTH and cortisone in man.[1285] Several workers observed no influence on anaphylactic shock or the Arthus reaction in intact animals,[470, 547, 793] although in one study [1842] mortality from anaphylactic shock was reduced. ACTH and cortisone, as well as salicylates, were capable of suppressing the Shwartzman reaction [1838]; they failed to alter the cutaneous reaction to histamine.[1285]

On the other hand, cortisone was found to depress the Arthus reaction and completely to prevent arteritis and carditis in eight of nine rabbits treated with horse serum.[1800] Rich and his collaborators found horse serum hypersensitivity to produce well-marked vascular or cardiac lesions in only five of 20 ACTH-treated rabbits, as compared to 18 of 20 untreated controls,[142] and in only four of 20 cortisone-treated rabbits as compared to 17 of 20 controls.[1675] It is of interest that renal lesions, with severe glomerular damage but without glomerular tufting, occurred in hyperimmunized rabbits receiving cortisone. The changes in mesenchymal tissues produced by cortisone treatment in hyperimmunized rabbits, with regression of accumulations of plasma cells and a transition in cytoplasm of reticulum cells to a hyaline substance, were interpreted as a change in serologic defense reaction from an active to an inactive stage.[2041]

[Obviously, further work is necessary to define the influence of cortisone and ACTH on immune mechanisms. "Whether this effect occurs at the level of antibody production, at the level of union of antigen and antibody, or at any other point in the development of the immune response is not established" (Fischel [547]).—Ed.]

Effect on Connective Tissue and on Inflammation. The failure of certain patients under ACTH and cortisone therapy to develop normal granulation tissue in open wounds led Ragan and collaborators [1628] to investigate the effect of cortisone on experimental wounds in rabbits. Development of granulation tissue was markedly delayed by systemic cortisone, with suppression of all new elements of connective tissue. The healing of experimental fractures also was delayed by cortisone.[100] Subsequent studies by this group [941, 1581, 1629] indicated that the rat is less susceptible to this effect than the rabbit, that the degree of suppression of granulation tissue varies with the dosage of cortisone used, and that such suppression follows local application of cortisone to wounds. It was suggested that the hyperadrenal state blocked the reaction of connective tissue to trauma, and that an analogous blocking of the reaction to an unknown irritant could account for the beneficial effects of cortisone in "mesenchymal diseases." Impairment of angioblastic as well as fibroblastic proliferation was noted in the above studies. Local application of cortisone greatly inhibited the vascularization of the cornea caused by intracorneal injection of alkali.[1007]

Baker and Whitaker [74] applied adrenal extract and cortisone directly to experimental wounds in rats, and found striking interference with the formation of granula-

tion tissue, the effect being limited to the area of treatment. This effect was definitely greater if the area was pretreated before making the experimental wound, suggesting an effect on normal connective tissue as well as on granulation tissue. It was further demonstrated that percutaneous application of adrenocortical hormones caused atrophy of mesenchymal as well as epithelial structures in the skin, with reduction in the number of fibroblasts and apparent loss of substance of collagenous fibers, but without change in elastic fibers.[288] Development of a refractory state to the action of the hormones occurred when treatment was continued for 180 days.[288] Hansen [773] found the amount of free metachromatic ground substance and number of mast cells to be reduced in the skin of patients during ACTH treatment. [The conclusion that these findings represent a change in concentration of hyaluronic acid should be supported by further evidence.—Ed.]

Biochemical and Physiologic Effects. Not one of the manifold changes in body chemistry observed during administration of ACTH or cortisone, while seen in patients with rheumatic diseases as well as in normal subjects, has appeared to be specifically related to the therapeutic effect of these hormones. Because the 11-oxysteroids have the greatest if not the only antirheumatic activity, attention has centered particularly on attempts to correlate changes in carbohydrate and protein metabolism with clinical effects. When patients with coexisting severe diabetes and active rheumatoid arthritis were allowed to develop glycosuria, nitrogen loss in the urine, and ketosis by reduction of insulin dosage, there was no effect on the arthritis. When they were treated with ACTH or cortisone, there was marked improvement of the arthritis, whether manifestations of diabetes were exaggerated or controlled.[280, 1257] Carlstrom and Lovgren [279] felt that the effects of cortisone confirmed their previous thesis that rheumatoid arthritis was characterized by a disturbance of enzyme systems concerned with carbohydrate metabolism, especially adenosinetriphosphate (ATP). [The only factual observation offered in support was the authors' experience of a favorable effect of ATP administration on rheumatoid arthritis; others have not found ATP effective.—Ed.]

Urinary excretion of histidine was increased in patients with rheumatoid arthritis when either cortisone or ACTH was given,[1955] that of threonine and tyrosine was increased by either cortisone or ACTH, that of lysine by ACTH but not cortisone, that of arginine by neither.[221] [Increase of alpha-amino acids in the urine has been found in normal subjects following these hormones, but individual amino acids have not been assayed. Increased urinary excretion of histidine is characteristic of pregnancy, and has been observed in remissions of rheumatoid arthritis associated with pregnancy.—Ed.] The aminopeptidase activity of the plasma of two patients who responded to ACTH and cortisone decreased from elevated levels concomitantly with clinical improvement, but was unchanged in four patients who did not respond clinically. This determination was thought to reflect changes in clinical status and not necessarily hormonal effects.[1785] ACTH and cortisone appeared to have a nonspecific antipyretic action.[1040, 1651] ACTH induced a marked increase in capillary resistance to negative pressure in patients with rheumatic diseases; while this effect paralleled closely the eosinopenia induced, it did not necessarily parallel the clinical effectiveness.[1704, 1705]

It was repeatedly stated that therapeutic effects were obtained by these hormones in pharmacologic rather than physiologic doses. It was suggested, but not established, that a favorable response was due to the production of some measure of hyperadrenalism.[1627, 1765] Many agreed with Hench [849, 850] that these hormones had no effect on the cause of the diseases, but provided "a shield-like buffer against the irritant, known or unknown. How they accomplished their antirheumatic effect was, to use a Churchillian expression, 'a riddle wrapped in a mystery inside an enigma.' They did not extinguish the fire, nor, carpenter-like, repair the damage, but provided an asbestos suit in which the patient, like

Shadrach, Meshach and Abed-nego, walked unscathed in the furnace. If the protection was not discarded until the end of the natural duration of the 'fire,' the patient remained well" (Hench[850]). Essentially a modification of this concept was the possibility that, for some reason, the connective tissue in rheumatic diseases was relatively insensitive to the controlling effect of adrenal steroids, and required a larger amount than other cells in the body for normal function.[1765]

The great diversity of physiologic and clinical effects of adrenal steroids suggested some ubiquitous and fundamental but single action at the cellular level.[1765, 2057] "The consequences of cortical hormone action spread through the organism in a manner reminiscent of waves caused by the impact of a stone in a pool of water, but the point of impact of the hormone remains unknown for the present" (Ingle[957]).

Untoward Effects. The initial reports of the clinical effectiveness of ACTH and cortisone noted the occurrence of some features of hyperadrenalism.[853, 855] It was soon appreciated that such effects which did not have a favorable therapeutic implication were in reality physiologic alterations induced by these hormones, and that such terms as "side effects" or "toxic effects" reflected lack of appreciation of the broad biologic significance of these substances.[1906]

The most complete reports on the unfavorable effects of cortisone and ACTH are by Sprague et al.[1906] and Hench et al.[854] Clinical and metabolic studies on 33 patients "confirmed what had long been known or suspected. These hormones had the capacity when administered in sufficiently high dosage for a protracted period of time, to induce most of the clinical and metabolic features of Cushing's syndrome. The features so induced in varying combinations included rounding of the facial contour, hirsutism, acne, keratosis pilaris, muscular weakness, edema, amenorrhea, cutaneous striae, mental depression, impairment of carbohydrate tolerance, negative nitrogen balance, increased excretion of corticosteroids in the urine, and hypochloremic hypopotassemic alkalosis. Significant hypertension was observed in only one case, in which the patient probably had antecedent parenchymatous renal disease. In addition, metabolic studies disclosed that cortisone and ACTH increased excretion of creatine and uric acid in the urine and gave rise to a negative balance for potassium in some cases. Their effects on balances of sodium and chloride were variable, the usual pattern being retention of salt early in the period of administration of the hormone, followed by an increased excretion when administration was prolonged. In some cases there were slight increases in urinary excretion of calcium and phosphorus." [1906]

It was appreciated early that the severity of such effects was closely related to size of dose and to duration of administration; the frequency and severity of these untoward reactions were reduced by the use of smaller doses of cortisone.[178] "Currently the best protection against the development of significant undesirable effects is to use the smallest effective daily and total dose" (Hench[856]). [This statement cannot be improved on at the time of writing this review.—Ed.] It was soon observed that untoward hormonal changes were more likely to occur in women than in men.[175, 579, 854]

These reports were abundantly confirmed by nearly every paper appearing on the subject. Sodium retention and edema, while occasionally a problem (especially in dealing with rheumatic fever with congestive cardiac failure[1315, 1318]), was usually readily controlled by a low sodium diet and diuretics.[856, 857] Hypo-

potassemia with muscular weakness and even stupor [497] did occur occasionally, but could be prevented by using potassium supplements. [Severe potassium deficiency appeared to develop more often in treatment of disseminated vascular disease, possibly due to larger doses used or to the nature of the disease itself.—Ed.] Significant hypertension rarely developed.

While evidence of impaired utilization of glucose could be demonstrated by glucose tolerance tests in patients receiving larger doses of ACTH and cortisone, the feared complication of development of diabetes mellitus rarely materialized, and clinically significant disturbances of carbohydrate metabolism were not reported. Patients with preëxisting diabetes usually required an increase in insulin dosage for control.[177, 230, 1257] Negative nitrogen balance was infrequent in metabolic studies on a fixed diet with doses of cortisone commonly used for long term treatment,[1006] and most patients on unrestricted diets gained weight, with clinical evidence that this weight gain represented a laying down of new protoplasm. Mild degrees of rounding of the face, hirsutism and acne were usually not regarded as dangerous, but development of well-marked clinical features of Cushing's syndrome was an indication for reduction of dosage or discontinuation of hormones.[497, 857]

The psychologic effects of these hormones varied from moderate euphoria (usually considered desirable), to obvious mental stimulation, with insomnia and fluctuations of mood (usually considered indications for dosage reduction), and to frank psychoses of various types (usually demanding cessation of hormone administration and constituting a contraindication to its further use). Some of the psychotic reactions were believed to be an exaggeration of premorbid personality trends,[857, 897] but some were evidently an organic mental reaction related to physiologic changes.[897] Electroencephalographic changes were seen in 13 of 15 patients during ACTH therapy,[897] and in two during cortisone administration.[177]

Impairment of wound healing was noted in patients receiving moderate and large doses of these hormones.[122, 1627] [This has not been a universal experience. However, if surgical procedures are contemplated, it seems advisable that hyperadrenalism be kept at minimal levels and that sutures be left in longer than usual.[1623]—Ed.] The hyperadrenal state can mask clinical signs and symptoms of intercurrent disease, such as infections or perforation of a ruptured viscus.[742, 1623] [This is a real problem in long term therapy.—Ed.] In certain other complications observed during prolonged use of these hormones, it is difficult to know whether they should be attributed to the underlying disease, to the hyperadrenal state or to coincidence. The occurrence or aggravation of peptic ulcer (often as complications such as perforation or bleeding)[742, 1756] may not be more frequent in patients on ACTH or cortisone therapy, but temporal association and the known effects of hyperadrenalism suggest a possible relationship. Spontaneous fractures have occurred in elderly patients with severe osteoporosis,[178] but could be attributed to long-standing slight but persistent negative nitrogen and calcium balance. Both purpura [178, 1774] and thrombophlebitis [1315, 1318] have been noted during the use of these hormones; no consistent pattern of change in the factors concerned with blood coagulation could be detected.[1871] Hypercholesterolemia developed during prolonged treatment with cortisone and ACTH.[14] [Some of us (W. D. R., E. W. B.) have found elevation of plasma cholesterol in such patients to be nearly always associated with other evidence of depressed thyroid function, and to

be corrected by administering desiccated thyroid. Others have not been able to detect a consistent cholesterol elevation in patients on long term minimal dose therapy (C. R.), or have not found such hypercholesteremia to be associated with evidences of hypothyroidism (E. P. E.).—Ed.] The development of a refractory state to ACTH was demonstrated in rats [676] and occurred in one clinical case report.[497] There was strong but not conclusive evidence of antihormone formation in both of these reports.

Undoubtedly the most reassuring feature of the more common untoward effects of these hormones is the fact that they are reversible. In man, as in experimental animals,[2194] discontinuance of these agents is followed by subsidence of evidence of hyperadrenalism in a few weeks. But the withdrawal of these hormones frequently presents problems in itself.[854, 857, 1623] Some of the symptoms of weakness following abrupt cortisone withdrawal can be attributed to adrenal suppression and atrophy,[1905] and this may also contribute to the occasional severe exacerbation of the primary disease, or to difficulties in control of intercurrent infections. [The suppression of endogenous adrenal function also seems to be completely reversible, normal function being reëstablished usually in two weeks, rarely as long as six weeks. Analogous suppression of pituitary function by ACTH can be suspected but has not been proved; clinical and metabolic observations suggest that, if it occurs, recovery is obtained in a few days.—Ed.] To minimize this problem, gradual tapering off with successively smaller daily doses of either of these hormones, or concluding a course of cortisone with a few days of ACTH administration, has been recommended.[857, 2055]

The undesired effects of cortisone and ACTH were regarded as "not alarming, but sufficiently dangerous to demand the closest clinical and laboratory observation of patients under therapy." [1348] They were "now assuming their proper position as features for which physicians must show respect and not fear" (Hench [849]). [It can be reasonably stated that since the time covered by this review nearly all of the untoward effects encountered in using these agents for a few weeks or even a few months can be handled by regulation of dosage and simple adjuvant measures, dependent on careful clinical observation. But with attempts to use these hormones to control chronic diseases over a period of years, the possible production of osteoporosis, development of peptic ulcer, fear of masking intercurrent infection or disease, and the attainment of a balance between undesirable effects and reasonable control of the disease present problems which are not yet solved.—Ed.]

Rheumatic Fever

Occurrence. It was again reported that approximately 2 per cent of school children in the United States have rheumatic heart disease, that 80 to 90 per cent of all heart disease below the age of 20 is due to rheumatic fever, and that rheumatic fever annually causes more than 10 times as many deaths as poliomyelitis. There was much less rheumatic fever during World War II than in World War I.[1608] Seven hundred patients with rheumatic fever and approximately the same number with rheumatic heart disease were hospitalized in 17 hospitals of the Mediterranean Theater of Operations, where these conditions accounted for 3.9 per cent of the 30,193 patients who were returned for medical disability.[159] Civilian mortality rates in England also declined.[653] The incidence of rheumatic heart disease in Canada was estimated to be approximately 1 per cent, based on an average of 16 cities. From 1926 to 1944 there was a striking decline in deaths

from heart disease in individuals below the age of 19 years, which was interpreted as a rough index of rheumatic heart disease. No such decrease occurred in ages 20 to 39.[1048]

In Idaho the determination of the prevalence and incidence of rheumatic fever from 1945 to 1947 permitted the following predictions: For each mean annual death per 10,000 of the population, all ages, attributed to rheumatic fever, there will be approximately the following numbers per 1,000 of the population, ages five to 19: individuals with definite history of rheumatic fever, 18 (prevalence); with definite rheumatic heart disease, 4.7 (prevalence); developing definite rheumatic fever for the first time each year, 1.4 (incidence); and having recurrences of rheumatic fever each year, 0.4.[427] In Denmark, where rheumatic fever is reported weekly, the incidence is declining; in Copenhagen it fell from 30 per 10,000 people in 1900 to 4.8 in 1946.[314] [Most observers agreed that the incidence and actual severity of the disease are decreasing, but that no accurate figures are available because of inadequate reporting or registration systems in most parts of the world.—Ed.]

Predisposing Factors Governing Incidence. *Geography and Climate.* Reports on prevalence or incidence of rheumatic heart disease or rheumatic fever are summarized in table 4, arranged in ascending order of incidence according to nature of sample analyzed and geographic distribution. [It is obvious that climate is affected by many factors in addition to latitude, and that there are nongeographic environmental differences as well as racial differences among the groups listed.—Ed.]

TABLE IV

Occurrence of Rheumatic Heart Disease in Various Geographic Areas

Location	Nature of Sample Studied	Incidence or Prevalence of Rheumatic Heart Disease	No. Examined	Reference
		Per Cent		
Iowa	School children	0.27*	5,058	967
Florida	School children	0.50	1,001	1759
Colorado	School children	1.0	1,017	2140
Georgia (Dublin)	School children	1.0	401	1607
Utah	School children	2.1	771	2243
Connecticut	Selective Service	0.75	100,000	2093
Panama	Hosp. Med. Admissions	0.06	228,748	775
Fiji (Fijians)	Hosp. Med. Admissions	0.2	1,162	93
(Indians)	Hosp. Med. Admissions	1.2	2,067	93
Puerto Rico	Hosp. Med. Admissions	0.4	10,388	583
	Hosp. Med. Admissions	1.0	5,000	583
Venezuela (Curaçao)	Hosp. Med. Admissions	1.7†	3,391	809
Tennessee	Hosp. Med. Admissions	2.8	4,750	1124
Panama	Autopsies	0.09	8,905	775
Louisiana (New Orleans)	Autopsies	1.35	12,317	2085
Louisiana (New Orleans)	Autopsies	1.4	8,313	916
Venezuela (Curaçao)	Autopsies	1.4	1,307	809
So. Africa (Bantu)	Autopsies	3.5	3,000	118
Ohio (Cleveland)	Autopsies	6.0	2,000	2128
Mexico (Mexico City)	Autopsies	11.0	2,000	1703
North Carolina	Autopsies	9.0	582	1359

* Prevalence of rheumatic fever was 0.61%.
† Rheumatic fever, not rheumatic heart disease.

Season. The highest incidence in the temperate zone occurs during the winter and spring. No seasonal incidence was observed in Panama.[775]

Social and Hygienic Factors. Emphasis was placed again on increased incidence among the low-wage groups and poverty-stricken families. The factors influencing the incidence of rheumatic fever in these groups were those conducive to the spread of hemolytic streptococcal infections, such as crowding, dampness and other conditions which are prominent features of poverty.[1538] In Connecticut, a comparative environmental and sociologic study was made of two localities within a few miles of each other which had rheumatic fever prevalence rates, among school children in the seventh and eighth grades, of 6.0 and 2.5 per cent, respectively. In the high-rate area the housing was of significantly poorer grade than in the low-rate area. Furthermore, in the low-rate area there was much more crowding in the homes of those who acquired rheumatic heart disease than in the homes of those who did not. Crowding seemed more important than a substandard home.[1613]

Family, Heredity and Constitution. Additional papers appeared in support of a genetic factor in susceptibility which behaves as a recessive Mendelian characteristic. A combined genetic age risk table was constructed on the basis of 109 families which can be used to predict the annual incidence of case onsets of primary and secondary attacks throughout the lives of these families. It was conceded by the author that such tables of prediction based on genetic and age factors alone should be tested in areas other than New York, where the incidence rates are lower.[2180, 2181] A positive family history was obtained in 8 per cent of 221 cases of rheumatic fever in a northwest Naval Hospital,[1287] and in 17 per cent of 225 cases in Virginia.[1841] Based on the observation of several thousand patients in the Armed Forces, Griffith stated that what has been called hereditary susceptibility to rheumatic fever may be largely due to poor nutrition and to crowding.[715] The occurrence of rheumatic fever in the family increases the risk of the individual's developing the disease while still in contact with the family, but not after he is separated from it.[721] In addition to hereditary traits, other things "run" in families, and factors which favor spread of contact infection in families must be considered in evaluating the familial prevalence of this disease.[1588] [The present viewpoint of the majority of the students of this disease may fairly be stated as a belief that there may be an inherited susceptibility, but that environment, specifically infection by the Group A hemolytic streptococcus, plays the major rôle.—Ed.]

Sex. Reports continue to reveal an approximately equal incidence between the sexes, if one excludes chorea.[974]

Age. The peak incidence of onset continues to be between the ages of six and eight years in this country. The disease, however, occurs from infancy to old age.[974, 1588, 2181] An initial attack at age 65 was reported.[46]

General Clinical Data and Relative Incidence of Manifestations of Rheumatic Fever

Of 689 patients with rheumatic fever studied by Jacobsson[974] in Stockholm, the initial manifestation of the disease was arthritis in 521 (75 per cent), chorea in 127 (18 per cent), and carditis alone in 41 (6 per cent). Of 266 military patients with rheumatic fever, all showed arthritis in some form, and all had fever; 73 per cent developed knee effusions, 63 per cent chilly sensations, 23 per cent epistaxis, 45 per cent cardiac abnormalities, 6 per cent skin lesions, and 2 per cent subcutaneous nodules.[325] Of 1,160 patients with rheumatic valvular involvement, joint pain occurred in 51.4 per cent, tonsillitis in 50.6 per cent, epistaxis in 28.7 per cent, and 44 per cent developed cardiac failure.[356]

Chief signs of active carditis were listed.[2215a] The appearance of a third heart sound for the first time during an attack of rheumatic fever presaged the appearance of an apical diastolic murmur.[612]

Erythema marginatum (erythema annulare) was specific for rheumatic fever; erythema multiforme and erythema nodosum were not.[640, 718] Erythema marginatum occurred in 5.8 per cent of 689 patients.[974] Petechiae appeared at an earlier age and in greater numbers in rheumatic as compared with nonrheumatic children who had frequent colds or who attended allergy or general medical clinics.[228] Rheumatic glomerulonephritis associated with carditis, peritonitis and pneumonitis was observed in one case.[1688]

Bruetsch[239] applied the term "rheumatic brain disease" to the degenerative mental changes due to rheumatic obliterating endarteritis. These may occur months or years following an episode of acute rheumatic fever. Cerebral involvement may vary from acute fulminating and violent psychoses in the active phase of the disease to the more protracted psychoses developed weeks or months after the acute rheumatic episode.[2087] Convulsive seizures caused by rheumatic brain disease and associated with rheumatic heart diease were reported in five cases. The convulsions began at an average age of 38, 10 to 32 years after onset of rheumatic fever.[2164] Five patients with rheumatic encephalitis were observed in 207 cases of rheumatic fever seen during a three year period at an Army Air Force base. All made a satisfactory recovery, although in two instances, six months or more were required.[2121]

Pathology of Rheumatic Fever

Cardiovascular System. Definite vascular lesions were observed in the heart, lungs, spleen and kidneys. The nature of the tissue damage seemed to be fundamentally the same, showing only modifications in different sites dictated by the essential structure of the tissue involved.[1355] Three instances of sudden and dramatic death, observed in a group of 7,165 convalescing cases of rheumatic fever, were ascribed to an acute anaphylactic coronary angiitis superimposed on a low-grade rheumatic carditis.[720] Severe and fatal forms of rheumatic pancarditis were described.[271] In a series of 3,000 consecutive autopsies on colored patients in South Africa, rheumatic heart disease was found in 106 cases. In 20 per cent, evidence of pericarditis was found, which in about one-half the cases was of the chronic constrictive variety.[607]

Joints. The present knowledge of joint pathology in rheumatic fever, as well as the pathology of the internal organs, was reviewed.[2096] The inflammation in the synovial membrane was essentially granulomatous, characterized by degeneration of the collagenous tissue and a monocytic infiltration.[39]

Nodules. The appearance of rheumatic nodules was of greater prognostic than diagnostic significance, since they suggested a severe and protracted form of the disease.[640] In 689 patients, subcutaneous nodules occurred at some time during the course of the disease in 5.4 per cent. The mortality rate was higher among the patients showing subcutaneous nodules.[974]

Subcutaneous nodules, indistinguishable from spontaneously occurring nodules, were artificially induced in rheumatic fever patients by subcutaneous injections of whole blood, saline, hyaluronidase[1316] and trypsin.[1411] It was concluded that the development of nodules results from injury to the subcutaneous fibrous tissue, the

reactivity of which is altered by the rheumatic process. The readiness with which nodules could be induced, and their size and duration, correlated closely with the degree of activity of the rheumatic process. It appeared that the blood of active rheumatic patients did not contain a nodule-stimulating substance. Other workers [1784] failed to produce subcutaneous nodules by injecting whole blood, trypsin or rheumatoid synovial fluid over the olecranon of patients with active rheumatic fever or rheumatoid arthritis, or of healthy persons.

Lungs and Pleura. Priority in the description of rheumatic pneumonia was claimed for Burnet by virtue of his description in a "Manual of Children's Diseases," published in Scotland in 1905.[255] In six fatal cases the clinical picture was marked by an acute onset of the pneumonic process, profound respiratory distress in the absence of equivalent physical findings, with pleural pain, hacking cough, scanty blood-streaked sputum, moderate to high fever, leukocytosis and x-ray evidence of a bilateral, multilobar, nonsegmental infiltration, which resembled pulmonary edema. There was no benefit from salicylate therapy. All cases were associated with rheumatic carditis. At autopsy, the cut lung surfaces did not exude frothy serosanguineous fluid, as occurs in acute pulmonary edema.[1802] Other cases having these features were reported and the differential diagnosis was discussed.[999, 1207]

Liver. Positive cephalin flocculation was found in 72 per cent of 136 cases of rheumatic heart disease. There was, however, no correlation with the age of the patient, duration of the disease, type of valvular involvement or degree of functional cardiac impairment.[1107] In six cases of rheumatic heart disease associated with cirrhosis and anemia, the cirrhosis was interpreted to be the result of the rheumatic heart disease.[490]

Kidneys. The relationship between acute rheumatic fever and acute glomerular nephritis was described, and three cases of acute purpura were reported, one associated with rheumatic fever, one with acute glomerular nephritis, and a third in which both conditions developed.[1008]

Nervous System. Cerebral lesions of rheumatic encephalopathy were described in detail by Costero [359] of Mexico. He believed these to be responsible for the death of all the children and many of the adults under his observation who succumbed to rheumatic fever. The lesions consisted of (1) profound alteration of the capillaries throughout the brain, causing increased permeability, followed by dilation of the lymphatic spaces, leading to cerebral edema and capillary sclerosis; (2) numerous microscopic hemorrhages in white matter, basal ganglia and the pons; (3) areas of destruction most prevalent in the cerebral cortex, due to intense mobilization of microglia; (4) foci of softening; (5) nodules of branching microglia in the gray matter of the pons, occurring less frequently than the other changes but considered by the author to be specific for rheumatic fever. Rheumatic lesions in the brains of 10 children who had died of acute rheumatic episodes were described.[1469]

Laboratory Data

Electrocardiographic Studies. Serial electrocardiograms during the active phase of the disease are essential if tracings are to be of maximal aid in diagnosis. Records were obtained every second day during the first week of illness and twice weekly thereafter in 62 young white soldiers, ages 17 to 21, suffering from a first attack of rheumatic fever. "Abnormalities" were seen within the first two weeks after onset of clinical symptoms in 98.4 per cent.[157] One case with frequent tracings illustrated how rapidly changes can occur.[2147]

In young adults, abnormalities in the electrocardiogram were the most frequent evidence of carditis. Of 700 naval patients with rheumatic fever, 147 (21 per cent) showed abnormal tracings.[1882] Changes in rhythm, myocardial changes and alterations in heart size were reflected in the electrocardiograms, and repeated tracings often were helpful in determining the activity of rheumatic fever. These findings may be transient.[1822] The three most common indications of rheumatic carditis were (1) shifting P-R time, especially if over 0.24 second; (2) the typical S-T changes of pericarditis; (3) the QRS and T changes occurring with myocardial damage due to anoxia resulting from coronary arteritis.[715] Four cases of rheumatic fever showed interference dissociations.[1935]

Several studies were concerned with prolongation of the Q-T interval in rheumatic carditis. The corrected Q-T interval (QT_c) was significantly prolonged in all of 50 children in the active phase of rheumatic fever.[2029] When a slightly higher upper limit of normal values was employed,[5] 90 of 100 patients with active carditis showed prolongation of QT_c. Other studies reported a lower incidence of this abnormality during active carditis: in only 70 per cent of 50 patients with active rheumatic fever up to the age of 20 years,[1584] and in 38 per cent of 229 electrocardiograms taken during active carditis compared with 27 per cent of 96 tracings taken during inactive rheumatic heart disease.[511] The incidence of QT_c prolongation found in the latter study was no greater than the incidence of accepted abnormal electrocardiographic evidence of active carditis. Some concluded that the usefulness of Q-T interval was minimized by technical difficulties in its measurement and by the infrequency with which it was abnormal in cases of pancarditis.[885]

In a follow-up study in Stockholm on 532 patients, nearly all under 30 years of age, who had rheumatic fever more than four years previously, and who were presumably not suffering from active disease, electrocardiograms were abnormal in 20.5 per cent.[974] Of 80 children with early valvular rheumatic heart disease who were examined after all evidence of active rheumatic fever had subsided, only 31.3 per cent showed abnormal electrocardiographic findings.[2156]

Sedimentation Rate and Alterations in Serum Proteins. Many papers again emphasized the importance of the sedimentation rate as an index to activity. However, the limitations of this procedure prompted investigation of several nonspecific alterations in serum proteins which reflect inflammatory disease and which may serve as more sensitive and reliable indicators of the rheumatic process. Minute quantities of C-reactive protein (an abnormal protein which appears in serum in the presence of any inflammatory disease) can be detected in human sera by a capillary precipitin test, employing a rabbit antiserum to crystalline C-reactive protein of human origin. The presence of C-reactive protein in the serum of patients with rheumatic fever was considered the most sensitive and the most consistently positive laboratory test for the presence of rheumatic activity that we now possess.[35]

The Weltmann serocoagulation reaction also proved to be a valuable laboratory adjunct in the detection of rheumatic activity. In 2,552 observations upon 400 patients (in the Navy) with or convalescent from rheumatic fever, the Weltmann reaction correlated with the clinical status 97.2 per cent of the time, against a correlation of 86.6 per cent for the Cutler sedimentation rate.[1464] Elevations in the level of serum mucoproteins also paralleled the degree of activity of the disease process; levels were not significantly elevated in uncomplicated chorea, inactive rheumatic fever, or in nonrheumatic children with uncomplicated acute streptococcal pharyngitis.[1047] Plasma hexosamine, which reflects a nonspecific response to tissue injury, was elevated in all

of 21 patients with acute rheumatic fever. Three patients with chorea had normal values.[1721] Elevation of serum complement occurred at the onset of a rheumatic attack, or shortly thereafter, in 45 out of 50 patients with rheumatic fever.[850] A paradoxic drop in the sedimentation rate during active rheumatic fever, together with enlargement of the liver, strongly suggested beginning cardiac failure due to active carditis.[496]

Alterations in the electrophoretic patterns of serum proteins of rheumatic and nonrheumatic children were studied in relation to antecedent respiratory infection. Elevation of the gamma globulin component appeared to be not a function of the rheumatic process but a reflection of previous infection, since there were no differences in the patterns of the two groups following respiratory illness. Increase in the alpha globulin fraction was usually observed during febrile periods of rheumatic activity.[2184] Changes in fibrinogen and gamma globulin were also studied by fractional precipitation of proteins with ammonium sulfate. By this method abnormalities in serum proteins were always demonstrable in the presence of gross disease and were more consistently abnormal than the sedimentation rate.[1196]

Hematologic Findings. A number of general reports emphasized that anemia is important as an early finding in active rheumatic carditis. Leukocytosis is generally recognized not to be a very good guide in determining rheumatic activity. Plasmocytosis of the bone marrow was found regularly in patients suffering from acute rheumatic fever and in patients convalescent from streptococcal pharyngitis. This was positively correlated with the increase in serum gamma globulin demonstrated in these diseases. These findings were absent in patients with inactive rheumatic fever and in patients with chorea.[669]

Capillary fragility was found to be significantly increased in a group of patients having rheumatic fever, and was interpreted as further evidence that rheumatic fever is a disease of blood vessels.[1420] Bleeding phenomena were found to be present in 28 rheumatic girls, as evidenced by early menarche, prolongation of menses and shortening of the menstrual cycle. Capillary resistance was decreased in this group.[229]

Relationship of Rheumatic Fever to Other Diseases

Rheumatoid Arthritis. In a critical analysis of the relationship of rheumatic fever and rheumatic heart disease to rheumatoid arthritis and rheumatoid heart disease, Bywaters [263] concluded that rheumatic fever and rheumatoid arthritis are two separate diseases, each associated with its own type of heart disease. He believed that recurrent rheumatic fever could in rare instances leave in its wake a "chronic secondary polyarthritis" (Jaccoud type), resembling but distinguishable from rheumatoid arthritis.

Tendon crepitus was due to fibrosis of the palmar sheath. The synovial membrane of involved joints was normal, but biopsies showed fibrosis of subsynovial and capsular tissues, the site of rheumatic granulomata. Bauer [1305] was of the opinion that the Jaccoud type of arthritis was not really different from rheumatoid arthritis, and that rheumatic fever and rheumatoid arthritis are unrelated. In 1,500 patients with rheumatic fever, definite rheumatoid arthritis occurred in 0.5 per cent; an additional 0.8 per cent had mild chronic arthritis which could have been attributed to rheumatic fever or to rheumatoid arthritis. From this observation Ziller concluded that the incidence of rheumatoid arthritis was no greater in rheumatic fever patients than would be encountered in the general population.[1305]

[This topic, particularly with respect to the controversial problem of cardiac lesions in rheumatoid arthritis, is discussed further under "Pathologic Characteristics of Rheumatoid Arthritis" and "Relationship of Rheumatoid Arthritis to Rheumatic Fever."—Ed.]

Subacute Bacterial Endocarditis. Of 111 deaths due to rheumatic infection, only three were related to subacute bacterial endocarditis.[974] Of 1,000 rheumatic fever patients followed for 18 years, with a mortality of 30 per cent, only 31 patients developed bacterial endocarditis.[1009]

Scarlet Fever. Most cases of "postscarlatinal rheumatism" were recognized as being rheumatic fever. In 7,836 cases of scarlet fever in Navy personnel, the ultimate incidence of rheumatic fever was "surmised" to be about 10 per cent.[1358] The incidence was lower in other series.[484, 1877]

The Differential Diagnosis of Rheumatic Fever

All papers agreed that there is no specific test for rheumatic fever, and that its diagnosis and differential diagnosis must still be based on an extremely careful evaluation of all factors. Consideration of the major and minor manifestations as proposed by Jones in 1944 was emphasized as important in the diagnosis.[715, 741, 1044] Of 285 soldiers, all diagnosed as having rheumatic fever on admission to the hospital, the diagnosis was changed later to rheumatoid arthritis in 33. The presence of carditis, erythema, purpura, pleuritis, pneumonitis, rapid joint changes, and a response to salicylates had pointed to a diagnosis of rheumatic fever.[508] A prompt response to adequate salicylate dosage was considered the most important diagnostic observation in acute rheumatic fever.[325]

Among the conditions confused with rheumatic fever were rheumatoid arthritis, polyarteritis, lupus erythematosus disseminatus, undulant fever, osteomyelitis, subacute bacterial endocarditis, acute gout, septic arthritis, gonococcal arthritis and myocarditis, acute meningococcemia, Reiter's syndrome, sickle-cell anemia, leukemia, tuberculosis and appendicitis.[17, 187, 240, 296, 325, 594, 715, 741, 770, 1044, 1722, 1815] [The list of diseases that should be considered in the differential diagnosis emphasizes the need for a more specific test.—Ed.]

Course, Prognosis and End Results of Rheumatic Fever

In children a loud blowing apical systolic murmur transmitted to the axilla was considered to be diagnostic of organic mitral insufficiency even in the absence of cardiac enlargement, and the intensity of the murmur was of prognostic significance.[1147] When 144 children (average age at initial attack, seven years; average age at admission, 11 years), discharged with diagnosis of mitral insufficiency only, were traced eight years later, 13 had died as a result of rheumatic infection and seven had succumbed to bacterial endocarditis. Recurrences of rheumatic attacks had occurred in 63 per cent prior to the original admission and in 19 per cent following discharge. Additional organic valvular lesions or bacterial endocarditis developed in 48 per cent.

Over-All Mortality. The mortality rate among patients who have had rheumatic fever varies with several factors. One obvious determinant is duration since onset of initial attack. It was reported from Philadelphia that one fourth of rheumatic children were dead 10 years after onset, one third after 15 years and one half after about 20 years[58]; from New York, that one fifth of the children were dead 15 years after onset, one fourth after 20 years, and one third after 30 years[2183]; from Boston,

that 30 per cent were known to be dead 18 years after onset[1009]; and from Sweden, that 16 per cent were dead after 12 years.[974]

Severity of rheumatic fever may have diminished and/or treatment may have improved in the last 30 years, to account for a significantly declining death rate among patients with rheumatic heart disease. These optimistic reports, issued from England by Knowelden[1122] and from this country by Ash,[58] differed from the observation by Wilson and Lubschez,[2183] who found that a comparison of the mortality rates for children born before and after 1919 showed no difference attributable to improvement in general care and nutrition.

Heart Damage During Initial Attack. Whereas the mortality rate at the end of 10 years, observed by Ash,[57] was 24 per cent of all 537 patients who had rheumatic fever, it rose to 42 per cent of the 318 children who had developed rheumatic heart disease during the initial attack. This agrees with 43 per cent mortality among such patients observed by Jones[1009] 18 years following first illness. In contrast, Ash found that only 5 per cent of the patients who had escaped cardiac damage during the first attack were dead at the end of 10 years, and 77 per cent were free of heart disease. These results are comparable to those of Jones, who reported that after 18 years, 7 per cent of the group diagnosed as "potential" heart disease after the initial attack were dead and 60 per cent were free of heart disease. In another study, all of 171 patients who were discharged with "potential" heart disease were alive after eight years, and 87 per cent were free of rheumatic heart disease.[1147]

Type of Onset. Among children whose initial attack consisted of carditis, 98 per cent had rheumatic heart disease at the end of 10 years, whereas 63 per cent of those whose illness was initiated by polyarthritis and 42 per cent of those whose illness began with chorea developed organic heart disease.[57]

Sex. The mortality rate from rheumatic fever and heart disease in England and Wales from 1924 to 1938 showed an excess mortality in females of 20 to 25 per cent at ages five to 14, 15 to 25 per cent at ages 15 to 24, and 20 to 30 per cent at ages 25 to 34.[1122] This was in contrast to a report from New York, in which there was no significant sex difference in age-specific mortality rates.[2183]

Preservation of Normal Capacity to Work. Of all the patients who had rheumatic fever, 60 per cent were able to lead normal lives without limitations 10 years after initial attack. This was reduced to 56 per cent after 15 years and to 41 per cent after 20 years.[58] A more optimistic report stated that 90 per cent of patients who were 21 to 42 years of age at last observation were able to carry on their normal activity without circulatory symptoms.[2183] [This apparently excludes all surviving patients who were younger than 21 and all those who were dead at time of observation.—Ed.]

Recurrences. Two similar groups were studied for recurrence rates during the first year. One group received hospital treatment; the other group did not. Of 115 children treated in the hospital, 12 per cent had recurrences. Of 134 children not hospitalized, 35.8 per cent had recurrences. The hospital recurrence rates were still not as low as in patients receiving sulfonamide prophylaxis.[969] The importance of being alert to minor recurrences and methods of detecting them were discussed.[150,770]

Etiology and Pathogenesis of Rheumatoid Fever

Epidemiologic Studies. An imposing body of evidence continues to accumulate implicating the Group A streptococcus as the initiating agent of both first attacks and recurrences of rheumatic fever.[16, 392, 342, 521, 652, 1538, 1608, 1729, 1970, 2011, 2011a] The seasonal variation of the incidence of hemolytic streptococcus infections, the "barrack epidemics" of the war years, similar outbreaks in residential schools, and the observed high incidence of prerheumatic infections with the Group A

streptococcus were arguments again put forth to demonstrate the intimacy of rheumatic fever and the hemolytic streptococcus.[322, 652, 717, 881, 1430, 1608]

[Pertinent also to the epidemiologic data are the reports of reduction in the incidence of recurrences of rheumatic fever by continuous chemoprophylaxis in the rheumatic subject, and the prevention of attacks of rheumatic fever by prompt treatment of streptococcal pharyngitis with penicillin, reviewed in the section on prevention of rheumatic fever.—Ed.]

On the basis of epidemiologic studies, the generally accepted concept of inherited susceptibility to the development of rheumatic fever has been challenged. The occurrence of multiple family cases was explained either on the basis of common environment or contagion.[717]

Bacteriologic and Immunologic Studies. The known characteristics of the Group A streptococcus and the immunologic responses to this organism were reviewed. Only Group A streptococcus has been shown to be associated with rheumatic fever, but no particular serologic type of this organism has been implicated.[1736] Of 73 patients with septicemia due to Group A streptococcus, only two developed clinical syndromes resembling rheumatic fever, and in these the diagnosis was questionable.[2018] Murphy and Swift[1451, 1452] reported that repeated focal cutaneous injections in rabbits with group A streptococci of diverse serologic types resulted in induction of myocardial lesions resembling Aschoff bodies, as well as endocardial and vascular lesions remarkably like those of rheumatic fever in man.

Antibody responses to several products of the Group A streptococcus were studied in rheumatic and nonrheumatic patients. Although these data added serologic support to the epidemiologic evidence for a relationship of the hemolytic streptococcus to rheumatic fever, they failed to identify any particular streptococcal product as a possible agent in its pathogenesis. There was agreement that, in general, patients with rheumatic fever show a more frequent, greater and a more prolonged rise in antibodies to various streptococcal antigens than do nonrheumatic patients following streptococcal respiratory infections. However, it appeared that the development of the rheumatic state was not accompanied by patterns of antibody response to any given antigen that differed from the general immune response to the same infection. The specific antibodies which received particular attention included antistreptolysin O, antistreptokinase (antifibrinolysin), antihyaluronidase, streptococcal agglutinins, type-specific anti-M precipitins and bacteriostatic antibodies, and antibodies against group specific C carbohydrates and streptococcal nucleoproteins.[84, 412, 794, 797, 798, 799, 801, 802, 1104, 1105, 1173, 1200, 1609, 1611, 1612, 1736, 2011, 2028]

The possible rôle of streptococcal hyaluronidase in the etiology of rheumatic fever received considerable attention, presumably because the substrate of this enzyme is hyaluronic acid, a mucopolysaccharide in the ground substance of connective tissues and also present in the capsule of some streptococci; some streptococci produce both hyaluronic acid and hyaluronidase.[1572, 1573] No antibodies against hyaluronic acid were demonstrated.[2011] The spreading effect of streptococcal hyaluronidase was found to be no greater in the skin of patients with active or quiescent rheumatic fever than in control subjects. Previous reports to the contrary were criticized on the basis of uncontrolled allergic inflammatory reactions influencing the spread of dyes in the skin.[800] In other studies using bovine testicular hyaluronidase, an increased spreading effect in the skin of patients with rheumatic fever, first reported by Guerra,[733] was confirmed by some[984] and denied by others.[1001] The inhibition by salicylate ingestion

of the spreading reaction of testicular hyaluronidase in animals and in man [732, 733] was confirmed in several reports [444, 1631] but not in others.[1001, 2013, 2014] Salicylates did not, however, inhibit the action of hyaluronidase in vitro except in very high concentrations beyond usual "therapeutic levels." [444, 614]

A nonspecific inhibitor of hyaluronidase which occurs in serum was described.[650] In contrast to species-specific antibodies against hyaluronidase, the serum inhibitor was heat labile, migrated with albumin rather than gamma globulin upon electrophoresis,[1421] and was active against hyaluronidase from different sources.[614] The nonspecific hyaluronidase inhibitor was elevated in serum during the active phase of rheumatic fever, and fell below normal during convalescence. The inhibitor behaved similarly in other inflammatory diseases but served as a fairly good clinical index of rheumatic activity.[443, 670, 696] Treatment of patients with ACTH resulted in a marked decrease in the level of inhibitor, paralleling the clinical course of the patient.[442] These results were not confirmed in another study in which oxalated blood was employed rather than serum.[512] [It has been repeatedly demonstrated that oxalate interferes with the hyaluronidase inhibitory activity of blood.—Ed.]

Studies on the serologic reactions to the streptococcal hemolysin, streptolysin S, revealed that this toxin, in contrast to streptolysin O, is not antigenic in man and animals and that there was no rise in serum inhibition during rheumatic fever or following Group A streptococcal pharyngitis; in fact, there was a fall during the acute phase of rheumatic fever.[949, 1967] This nonspecific serum inhibitor of streptolysin S appeared to be associated with lipoproteins and the fall in titer which occurs during acute rheumatic fever, and other inflammatory states, reflected a fall in serum lipids.[950, 1968]

Factor of Hypersensitivity. Several lines of investigation continued to attempt to relate the rheumatic process to hypersensitivity. One study appeared to confirm the "phase reaction." When the serum of a patient with acute rheumatic fever was mixed with the serum of a patient convalescing from the disease, a precipitate formed. Similar precipitation was found in other infectious diseases, but in a much lower titer.[2141] This "phase reaction," which implies the union of an unidentified antigen and antibody, was critically reviewed; it appeared to be an inconstant phenomenon, more likely to be related to a colloidal abnormality of serum than to a specific immune reaction.[549]

Further reports appeared on the experimental production of "autoantibodies" which presumably induced organ-specific lesions. Rats and rabbits injected with emulsions of tissues from the same species in conjunction with killed Group A streptococci commonly develop "autoantibodies" which react in vitro with extracts of homologous tissues. In rats such "autoantibodies" to kidney produced glomerulonephritis, while "autoantibodies" to heart or connective tissues led to cardiac lesions which "resemble those seen in rheumatic fever." Attempts to demonstrate specific "autoantibodies" to human tissue extracts by complement fixation or collodion particle agglutination technics were unsuccessful.[292, 293, 1065] False-positive reactions and variable results with the same test sera on different occasions were noted.[549]

Numerous reports demonstrated the gross and microscopic resemblance of the pathology of experimental serum sickness in animals to the lesions of rheumatic fever. Horse serum sickness in rabbits [1162, 1354, 1676] received particular attention. The term "protein carditis" was applied to the changes produced in experimental animals. In mice, injection of egg albumin was followed by lesions bearing a "striking" resemblance to those of rheumatic fever. Similar morphologic changes in normal control mice were observed, but were of minimal intensity.[1422] Injection of albumin-bacterioplasma conjugates into mice also resulted in "rheumatic fever-like lesions." The con-

jugates were then administered to a patient with rheumatic fever, resulting in exacerbation of the disease. In patients with inactive rheumatic fever, local reactions were observed in "high sensitivity levels," in contrast to the controls, where low levels prevailed.[1782] Gray[706] warned that mice are unsuitable for experiments designed to induce "rheumatic-like" lesions associated with anaphylactoid hypersensitivity, since she found spontaneous cardiac lesions in a high percentage of Swiss mice.

Prevention or significant reduction of the cardiac lesions in experimental serum sickness was demonstrated by treatment with salicylates,[1873] with antihistaminic drugs,[1160] with ACTH,[142] and with cortisone.[1675, 1800]

In one study the incidence of allergy in 100 rheumatic patients was three times that of a control group, and there was a higher incidence of allergy in the families of rheumatic patients than in those of the controls.[1883] Following an extensive review of the possible relationship of hypersensitivity to rheumatic fever, Fischel[546] concluded: "There is, as yet, no clinical test for the detection of an allergic reaction in rheumatic individuals that does not occur in patients recovering from a streptococcal infection or certain other diseases."

Nasopharyngeal and Other Infections. Nasopharyngeal or upper respiratory infections preceded the rheumatic fever in from 50 to 75 per cent of patients.[878, 1608] Of 214 patients with rheumatic fever who received careful nasopharyngoscopic examination, 75 per cent of those showing active rheumatism and 49 per cent of the convalescent group had abnormal nasopharyngeal findings, as compared to 32 per cent of 200 normal soldiers.[1735]

Group A streptococci were isolated from 2.7 per cent of routine throat cultures and from 33.3 per cent of excised tonsils of a group of patients with rheumatic fever, with no difference between the active or inactive groups. In nonrheumatic subjects, the cultures were positive from the throats in 3.1 per cent and from excised tonsils in 15.6 per cent. There was no evidence that tonsillectomy, followed by administration of penicillin postoperatively, had any adverse effects on patients with low grade rheumatic activity.[1464] Children without tonsils do not escape rheumatic fever in sufficient numbers to justify universal tonsillectomy as a preventive measure. Indications for tonsillectomy in rheumatic children were the same as in nonrheumatic.[1388]

Of 542 cases of rheumatic fever studied, precipitating factors other than the hemolytic streptococcus were noted in 55 cases. Fractures, burns, skin rashes, other infections, penicillin and tetanus toxoid were named.[1729] Smallpox vaccination was followed by definite reactivation of rheumatic fever in two patients and probable reactivation in two more of a group of six children.[593] [Subclinical streptococcal infection was not excluded by study of specific serum antibodies.—Ed.]

Virus Theory. Little comment was made on the possible virus etiology of rheumatic fever other than to note that there is no convincing evidence to support it.[632] Further research was urged, however, after a review of the evidence.[679]

Dietary Factors. Negative comments constituted the bulk of evidence regarding vitamin deficiency as a direct or indirect etiologic agent in rheumatic fever.[652] A thorough study of experimental scurvy led to the conclusion that there was "only a superficial morphologic similarity between the articular lesions of scurvy and those of either rheumatoid arthritis or rheumatic fever."[1877] The blood levels of ascorbic acid did not differ from those found in comparable nonrheumatic subjects on the same intakes.[2182] Large doses of ascorbic acid (4 gm. per day) seemed to have some antirheumatic activity in seven patients treated with this vitamin.[1319] Attention was called to the possible relationship of serum lipids to rheumatic fever.[323]

Relationship of Adrenocortical Function. Considerable speculation was aroused as to the rôle of pituitary-adrenal function in host susceptibility to rheumatic fever as

a result of the discovery of the dramatic suppressive effects of ACTH and cortisone on the rheumatic process.[2056] [As yet, however, there has been no definite evidence of abnormal adrenal cortical function in rheumatic patients, and the question awaits further clarification of the mechanism of the antirheumatic effects of the adrenal cortical hormones. —Ed.]

Conclusions on Etiology. The bulk of evidence offered since the last review adds considerable weight to the rôle of the Group A streptococcus as the major, if not the only, etiologic agent of rheumatic fever. The pathogenesis of the disease remains an enigma, however, and such factors as host susceptibility, possible changes in the characteristics of the streptococcus in its capacity to produce rheumatic fever, the mechanism of hypersensitivity reactions, and the influence of meteorologic factors deserve continued exploration.

Treatment of Rheumatic Fever

Rest and Exercise. All authors agreed on the absolute necessity of rest during the acute stage.[771, 1145, 1314, 2027] Nearly all interpreted rest as complete bed-rest. On the theory that rest does not necessarily mean confinement in bed, 200 young adults with rheumatic fever were allowed to do what they could do easily, the patient's comfort being the sole determinant of activity. They were allowed to sit in a chair for short periods, encouraged to use the toilet instead of bedpans, and provided with early occupational therapy. Meanwhile, full doses of salicylates were being administered to the patients. This regimen almost completely abolished cardiac neuroses, increased the percentage of men returned to duty, and, throughout the entire carefully followed series, showed no ill effects. While not warranting dogmatic conclusions, this experience invited attention to a reëvaluation of the currently accepted policy of prolonged confinement in bed.[1687] [This experience with military personnel may not apply to children with rheumatic fever. The relatively benign course of rheumatic fever in adults in contrast to children is well recognized.—Ed.]

Convalescent Care. With a reconditioning program based on a scoring system in performance of progressive tests, there was no increased cardiac disability.[1038] Earlier ambulation and graduated exercises were urged.[1687, 1781] Psychotherapy was essential in preventing the functional disabilities that occur from rheumatic fever.[12] Home surroundings and family relationships during convalescence were important.[862, 1840] When home surroundings were unsuitable, sanitarium care was essential.[154]

Salicylates. The opinion was almost unanimous that salicylates should be given orally rather than intravenously. The majority favored a large oral dose, achieving a blood concentration of approximately 35 mg. per cent, or given to the point of mild toxicity, indicated by ringing in the ears and slight deafness.[325, 715, 953, 975, 1286, 2026, 2122] Of those advocating large dosage, only Taran[2026] and Manchester[1286] continued to express the belief that high blood concentrations of salicylate, given early, will definitely alter the course of the disease and prevent cardiac damage.

According to most observers, the therapeutic value of salicylates in rheumatic fever is limited to their analgesic, antipyretic and antiinflammatory properties. The sedimentation rate was reduced by the drug but this action was not specific for rheumatic fever.[796, 1640] Bywaters[262] stated that salicylates mask evidence

of activity and do not prevent development of pericarditis, subcutaneous nodules or chorea during their administration. Death from rheumatic carditis and congestive failure was not avoided when salicylates were given.

Metabolism. Both therapeutic and toxic effects of sodium salicylate or aspirin are related to concentration of salicylate in plasma. A large part of the plasma salicylate is bound to proteins,[1868] and only the unbound portion is filtered by the glomeruli. Salicylate is excreted mostly as conjugates (salicyluric acid and glycuronides) of salicylic acid, and to a lesser extent as free salicylate. These forms accounted for 80 per cent of administered salicylate.[1868] In addition to these, part of the administered salicylate is oxidized to gentisic acid. In acid urine, the unchanged or free salicylate constituted 10 to 20 per cent of the total excreted salicylate, whereas at alkaline pH it composed about 52 per cent of the excreted salicylate.[903] [Salicylate fractions vary greatly from patient to patient and depend on pH of urine.—Ed.] The administration of sodium bicarbonate resulted in a substantial fall of the plasma salicylate level, mainly as a consequence of markedly increased excretion of free, unconjugated salicylate in an alkaline urine,[1868] attributed to a diminished tubular reabsorption of free salicylate from the glomerular filtrate.[903] Contrariwise, the plasma salicylate level may be increased by suppressing salicylate excretion, by decreasing tubular reabsorption or by blocking tubular excretion. Acidification of urine induces the former change, whereas administration of para-aminobenzoic acid accomplishes the latter.[458, 1731, 1751] Reid [1657] found that the level of plasma salicylate fell spontaneously after a few days of drug administration, even though the dose was kept constant, and he believed that relapses of rheumatic fever during salicylate therapy were often due to failure to maintain adequate concentration of plasma salicylate. [This observation is contradicted by results of others [904] and should be checked by further studies.—Ed.]

Salicylate medication caused only slight changes in blood prothrombin concentration, a moderate fall in serum bicarbonate, a slight fall in serum sodium, a rise in serum chloride, and essentially no change in pH.[904]

From balance studies in seven adult patients, Reid, Watson and Sproull [1658] concluded that clinical improvement and fall in sedimentation rate were the result of a shift in body water, first from the intracellular to the extracellular compartment, and later from the extracellular space by diuresis, changes initiated by increased protein breakdown induced by administered salicylates. Dehydration by other measures had produced similar results.[851] [The balance studies reported by Reid and associates seemed to us inadequate and the published evidence not sufficient to support the conclusions drawn.—Ed.]

Toxicity. Hyperventilation resulting from salicylate administration is due to reflex stimulation of the respiratory center and is independent of the blood acid-base relationship. Hyperventilation produces a respiratory alkalosis, later followed by reduction in alkali reserve of the blood.[902] The resulting early low values for carbon dioxide in the blood do not in themselves necessarily indicate need for alkali administration. However, during the subsequent period of therapy, when both carbon dioxide content and pH values are low, true (metabolic) acidosis exists for which alkali is specific.[459, 526] [This is not in conflict with the rationale of giving alkalies intravenously or orally in cases of severe salicylate intoxication, since alkalies are an effective means of increasing salicylate excretion.—Ed.]

Toxic symptoms were related primarily to plasma salicylate levels. Tinnitus, deafness, nausea and transient vomiting indicated that plasma concentration was approaching 35 mg. per cent, above which level unfavorable manifestations, such as mental symptoms, were more severe. [One of us, M. W. R., agrees that when sodium salicylate is used, a blood concentration of 35 mg. per cent is the optimal level; however, when aspirin is used, this is definitely a toxic level, and the optimal level is about 25 mg. per cent.—Ed.] Local gastric irritation, so often found with sodium salicylate, oc-

curred only occasionally with aspirin, and was avoided completely by using tablets containing aluminum hydroxide.[904] Aluminum hydroxide, unlike sodium bicarbonate, did not modify the serum salicylate level.[2143] Enteric-coated aspirin was useful in patients who could not tolerate regular aspirin because of local gastric irritation.[2024] In children, aspirin appeared to be more toxic than sodium salicylate.[459] Two deaths in children from acute aspirin poisoning were reported, with necropsy findings of damage to brain, kidneys and liver.[1228]

Cortisone and ACTH. The historic report on the striking effects of cortisone on rheumatic fever by Hench and his associates [859] enumerated the manifestations that were readily suppressed, such as fever, polyarthritis, tachycardia, "toxemia," anorexia, elevated sedimentation rate, impairment of atrioventricular conduction, anemia and hyperglobulinemia. In this preliminary report the authors warned that prolonged observation would be required "before it can be determined whether or not compound E has prevented or lessened development of chronic organic injury to the heart valves or myocardium." In subsequent reports by this group during the next 18 months,[91, 850, 854, 856, 857] additional observations included parallelism between the action of ACTH and cortisone, reduction in cardiac size, rapid subsidence of exudative reactions, and grounds for thinking that even the proliferative reactions might be suppressed, persistence of preëxisting organic murmurs but absence of new or of increased cardiac damage during hormone administration. It was also noted that rheumatic activity recurred when the hormone was withdrawn before the disease reached its natural termination, that the disease was not cured nor was its natural duration shortened, nor were recurrences prevented. Other investigators amply confirmed these observations.[9, 1316, 1320, 1347, 1348, 1349, 2056, 2057]

Following ACTH, signs of pericarditis with or without effusion disappeared in each of four cases in from one to 14 days. Chorea improved strikingly in one case, subcutaneous nodules softened, diminished or disappeared, and new nodules did not appear. Congestive failure was relieved in two of four patients, and significant cardiac murmurs disappeared rapidly in three cases. Some of these effects were attributed to an antiinflammatory effect on the myocardium. In three cases, relapse following withdrawal of ACTH spontaneously subsided.[1320] Massell [1315] concluded that ACTH suppressed the rheumatic process more promptly and completely than any other therapeutic agent and in some cases terminated the rheumatic attack. McEwen and his associates [1349] suggested that the results may be roughly related to the time at which therapy is instituted. In general, patients treated early responded more favorably than those treated much later in their disease. However, four patients in whom hormone therapy was begun within 14 days of the onset of the final attack developed evidence of persistent cardiac damage.[1348] [An important coöperative study is being conducted by the Council on Rheumatic Fever to determine the immediate and ultimate course of the disease when treated with these hormones. Successive cases, carefully matched with respect to those factors known to influence the course of the disease, are receiving a standardized dosage of cortisone, ACTH or salicylates. A preliminary report in 1952 indicated no apparent difference in the course of the acute episode of rheumatic fever among the three groups. This study can be expected to yield authoritative information as to the frequency and severity of cardiac damage within a few years.—Ed.]

In 18 patients with rheumatic carditis who were given ACTH or cortisone,[1347] the "C" reactive protein, fibrinogen and gamma globulin returned to normal levels. The size of the heart decreased in only one case. Most of the patients experienced a self-limited reactivation of rheumatic fever after hormone was discontinued.[1347] Although the serum mucoproteins, nonspecific hyaluronidase inhibitor and sedimentation rate were elevated and parallel to each other during the course of rheumatic fever, when ACTH or cortisone was given the hyaluronidase inhibitor and sedimentation rate rapidly returned to normal, but the mucoprotein level fell quite slowly,[9] suggesting that during hormone therapy the mucoprotein was a more reliable guide to persistent rheumatic activity than other laboratory findings.

Other Drugs. Gentisic acid, an oxidation product of salicylate, inhibited hyaluronidase in vitro in much smaller concentrations than did salicylate. In daily doses of 10 to 18 gm., sodium gentisate was followed by improvement in patients with rheumatic fever and rheumatoid arthritis.[1378, 1768] Meyer and Ragan [1378] suggested that the antirheumatic action of salicylate was due to its oxidation product. Glucuronic acid, a constituent of mucopolysaccharide in the ground substance of connective tissue and also used by the liver for detoxication, was administered as calcium, potassium and sodium salts to patients with rheumatic fever and other rheumatic diseases with "Very satisfactory results" in most instances.[1559] [These results have not been confirmed in more recent studies.—Ed.] Calcium succinate combined with aspirin was advocated, and described as a respiratory catalyst, improving tissue oxidation. Thirty-four cases of rheumatic fever were so treated.[2018] Succinate compounds and ascorbic acid administered to patients with rheumatic fever were uniformly ineffective.[646, 2144] Hydroxy phenylcinchoninic acid was found to control promptly the fever, malaise and arthritis of 10 patients with severe acute rheumatic fever. It did not, however, terminate the attack in all cases, and the effect on heart disease was uncertain.[158] In 39 cases of rheumatic fever treated with vitamin P, there was a definite slowing of the sedimentation rate, and a probable beneficial effect upon the disease.[1681] Vitamin P was extremely effective in reducing nosebleeds in rheumatic fever.[1138] Ninety-seven patients with active rheumatic fever were treated from 1938 to 1950, first with chorionic gonadotropin, and later with progesterone (500 mg.) and estradiol (33.3 mg.), injected intramuscularly two to seven times at intervals of four to eight days. Satisfactory response was reported in 58 per cent.[212] [Not enough data are presented to permit independent critical evaluation.—Ed.]

Ultraviolet Blood Irradiation. The acute rheumatic state in 22 consecutive hospital patients with severe carditis terminated in three weeks or less following ultraviolet blood irradiation. By the same measure, recurrences of rheumatic fever were believed to have been prevented in 107 of 109 cases over a period of two to four years.[2130] [No controls were used, no case reports given, no detailed physical findings, anatomic diagnoses or laboratory results recorded. From the published data it is impossible to evaluate the results independently.—Ed.]

Nutrition. For children with rheumatic fever, the following diet was recommended: low in fat, high in protein and carbohydrate, to include daily one quart skimmed milk, 15 mg. of iron, 5,000 units vitamin A, 400 units vitamin D, 100 mg. vitamin C, and double the standard allowance of vitamin B complex; no restriction of water intake. In cases of congestive failure, sodium intake should be restricted to 1 to 3 gm. Repeated small transfusions should be administered when the hemoglobin is less than 9.0 gm. per cent.[968]

Special Treatment for the Heart. In children with the early anoxic phase of acute rheumatic carditis, inhalation of 40 to 60 per cent oxygen resulted in clinical improvement and return of the Q-T : T-Q (systolic : diastolic ratio towards normal).[265, 795, 1961, 2030] When need for diuresis was urgent, mercurial diuretics in conjunction with ammonium chloride were very effective.[265, 325, 337, 496, 795, 2026] Otherwise, xanthine derivatives were preferred.[1314] In the presence of congestive failure, digitalis was found to have little or no effect[1314]; in some cases, ill effects outweighed the benefits.[2027] It was useful in auricular fibrillation. [Most authors feel that digitalis should be used if indicated.—Ed.]

In a controlled study, x-ray irradiation through the myocardium and cervical ganglia appeared to be of no value.[719]

Prevention of Rheumatic Fever

Sulfonamide Prevention of Recurrence. Rosenberg and Hench reviewed reports from 10 investigators covering 1,037 patient-seasons of sulfonamide prophylaxis, and 1340 patient-seasons without sulfonamide prophylaxis. There were six times as many recurrences and twice as many deaths among the group not on prophylaxis.[1728] [The details of these reports are also available in the last Review.—Ed.] Since this summary, other studies have supported the effectiveness of sulfonamide prophylaxis. Two hundred sixty-eight additional patient-seasons have been recorded, with similar evidence for the successful use of sulfonamide prophylaxis in this country.[81, 82, 1264, 1265, 2201]

Wilson[337, 2181] found these reports unconvincing from a statistical viewpoint, due to inexact matching of treated and control series, largely with respect to age and to time elapsed since the last active rheumatic infection. Because of this criticism, others have expressed the opinion that the evidence for sulfonamide prophylaxis is as yet inconclusive.[337, 1961, 2026] These objections were specifically answered in a large and admirably controlled study conducted in Australia in which control and treated groups were carefully matched. There were 971 person-years studied in the control group and 565 person-years in the group treated with sulfanilamide. For children aged four to 14 years, a recurrence rate of 11.8 per cent was observed in controls and 3.2 per cent in the treated group.[1741] These results closely parallel the consolidated reports of previous workers which show recurrence rates of 13.7 per cent for control groups and 2.2 per cent for treated groups. It was further concluded that chemoprophylaxis must be considered for *all* patients with rheumatic fever, irrespective of the severity of the first attack, since the initial severity of the disease does not determine the subsequent recurrence rate. [Fourteen different groups of investigators have shown striking reduction of recurrences with the use of sulfonamide prophylaxis.—Ed.]

Toxic reactions continued to be mild. However, close observation of children on prolonged sulfonamide prophylaxis was urged.[82, 1265, 1741, 2201] It was generally recommended that sulfonamide prophylaxis be taken throughout the entire year. Although sulfonamide-resistant organisms have appeared during large scale prophylaxis in military establishments,[1558] the danger of dissemination of drug-resistant organisms was considered small in dealing with the small fraction of the population represented in treating rheumatic children.[1741] Furthermore, in the event of serious illness due to sulfonamide-fast organisms, other chemotherapeutic agents are available.

On two occasions an epidemic of sulfonamide-resistant infection developed in a convalescent home housing many rheumatic children. Prophylaxis was changed to oral penicillin in doses of 100,000 units twice daily, which prevented further outbreaks.[1264]

Penicillin Prevention of Recurrences. Despite the greater effectiveness of penicillin against Group A streptococci, there have been few extensive studies employing this antibiotic. Penicillin troches of 1,000 to 5,000 units were given three times daily, before meals, to 22 rheumatic children, with an equal number of children serving as untreated controls. None of the treated group developed a recurrence of rheumatic fever; of the control group, four developed attacks.[1264] In another study 64 children were treated with daily oral doses of 800,000 units for seven consecutive days during the first week of each month throughout the school year. A similar number were divided into two control groups. No recurrences occurred in the group treated with penicillin, in contrast to a recurrence rate of 11 per cent and 19 per cent, respectively, in the control groups during one complete season.[1125] In a convalescent home 155 children were treated for 23 months with 100,000 units daily by mouth, taken three quarters of an hour before breakfast. There were no rheumatic recurrences in this group, compared with four recurrences in a group of 145 controls. There was also a reduction in the incidence of streptococcal pharyngitis and carriers of hemolytic streptococci in the treated group.[520] In a careful study, penicillin was administered orally to 38 rheumatic children in a dose of 50,000 units twice daily on an empty stomach. An equal number served as controls. Three treated patients had recurrences, compared with six recurrences in the control group. The three treated patients who developed recurrences had no hemolytic streptococci in their throat cultures but showed an elevated serum antistreptolysin O titer. There were 52 positive throat cultures in the control group and only three in the treated group. Head colds occurred with about equal frequency in both groups.[213]

The effectiveness of orally administered penicillin against Group A streptococci was studied in rheumatic children who received doses of 100,000 units twice daily on a fasting stomach. Each dose was found to produce "satisfactory therapeutic blood plasma levels" for approximately three hours following each administration. None of 63 patients in the treated group had respiratory infections due to Group A streptococci, and one was found to be a confirmed carrier. In 64 controls, there were four streptococcal respiratory infections and 11 carriers.[599] When 50,000 units were given orally to rheumatic children, serum levels of 0.25 unit were obtained after one hour and 0.04 unit after two hours.[1295] [It has also been shown that the vast majority of strains of Group A streptococci which have been isolated are sensitive in vitro to 0.04 unit of penicillin or less.—Ed.] No toxic reactions were noted in any of these studies.

In no studies were penicillin-resistant strains of Group A streptococci isolated from patients receiving penicillin. A previous report of "penicillin-resistant streptococci"[1410] was criticized on the basis that no attempt had been made to group the isolated strains by the Lancefield precipitin technic.[899] Reviews of the literature have not revealed a proved instance of increased penicillin resistance of Group A streptococci associated with a human infection.[634] Although penicillin resistance of nonhemolytic streptococci isolated from the throats of children receiving prophylactic penicillin is increased, the resistance is not so great as that reported for some strains of nonhemolytic streptococci isolated from patients with subacute bacterial endocarditis who were successfully treated.[1136]

Prevention of Rheumatic Fever by Treatment of Streptococcal Infection. While the above studies concentrated on prevention of recurrences of rheumatic fever in rheumatic subjects, another approach to the prevention of rheumatic fever concerned the prompt treatment of streptococcal pharyngitis with penicillin. When 10 clinical and five subclinical streptococcal infections in patients with rheumatic fever were promptly treated with penicillin, there were no rheumatic recurrences. Orally administered penicillin, in doses of 30,000 to 1,000,000 units daily for 10 days, suppressed hemolytic streptococci in the throats of all but 2.1 per cent of patients with rheumatic fever during the period of treatment, and completely eradicated the organism in 77.7 per cent.[1217] Eighteen chronic carriers of beta-hemolytic streptococci and two patients with acute streptococcal tonsillitis were each treated with a total of 1,200,000 units of penicillin, given intramuscularly, over 10 successive days. In 17 cases the infecting organisms were eliminated from the throat culture. In five cases tonsillectomies were performed 125 to 185 days after treatment; the tonsillar fossae and sectioned tonsils were free from hemolytic streptococci.[657]

An extensive and important study indicated that rheumatic fever can be prevented in young adults by the treatment of streptococcal disease with penicillin. Streptococcal pharyngitis was treated either with 300,000 units of procaine penicillin given twice, three days apart, by intramuscular injection, or with 300,000 units of the same product initially, again in 48 hours, and 600,000 units 96 hours after the initial dose. Rheumatic fever developed subsequently in only two of 798 patients so treated. Of 804 who did not receive penicillin, rheumatic fever developed in 17. A rise in antistreptolysin O titer was usually suppressed and streptococci were eradicated from the throat in many of the penicillin-treated patients.[418] [Note: This is the first large scale controlled study on the prevention of first attacks of rheumatic fever.—Ed.]

The early treatment of scarlet fever with crystalline penicillin G was undertaken in 167 children, in an attempt to prevent subsequent rheumatic fever and glomerulonephritis. Twelve patients (7 per cent) developed mild manifestations suggestive of rheumatic fever; six of these (3.5 per cent of the total group) were considered to have developed definite rheumatic fever. No control group was compared.[2145]

Climate. It is generally conceded that initial attacks and recurrences are less frequent in subtropical climates. [No thorough statistical study, including sufficient patient years, has yet appeared in the literature.—Ed.] Eighty-eight children, aged six to 16 years, were brought from the north to Florida between the years 1938 and 1945, and spent a total of 114 patient-years there. During this period about the same number of colds, bronchitis, virus pneumonia, measles, mumps and chicken-pox occurred among the children as had previously been the clinical experience in the north. Severe streptococcal infections were conspicuously rare, despite the fact that throat cultures made each month showed 10 to 20 per cent incidence of beta hemolytic streptococci the year round. During this period only one typical recurrence was observed; it was very mild and lasted less than one week. Six of the seven total recurrences, judged by Jones's criteria, would have escaped detection.[1697] Change of climate should be considered only as a prophylactic measure, since fewer and milder recurrences of the disease usually mean less cardiac damage.[770, 1697]

Community Responsibility and Public Health Services. Many papers emphasized the importance of mobilizing community resources against rheumatic fever to aid prevention of the disease. Educational programs, designed for both

the profession and the laity, were urged. Case-finding and other public health methods similar to those which have been proved useful in tuberculosis are important weapons in the prevention of rheumatic fever. Adequate hospital and sanitarium facilities must be made available. Development of consultation clinics, better diagnostic facilities, requiring that the disease be reported, and follow-up studies were all urged.[287, 716, 862, 906, 1045, 1457, 1730, 1745, 2159, 2159a, 2233] The American Council on Rheumatic Fever is available for assistance in forming community programs.

[Since there are no effective measures for preventing cardiac sequelae once rheumatic fever develops, the need for preventing initial or recurrent attacks of rheumatic fever becomes imperative. Methods of prevention are dependent upon etiologic concepts. Clearly, prophylactic measures must be directed toward (1) preventing Group A hemolytic streptococcal infections, (2) altering the susceptibility of the individual, whether hereditary or acquired, and (3) changing the environmental factors. Since climatic change is practical for so few, and no method is known for altering susceptibility, the major stress in prevention of rheumatic fever has been placed on control of hemolytic streptococcal infections.—Ed.]

Sydenham's Chorea

This disease, regarded as one of the major manifestations of rheumatic fever, was thoroughly reviewed.[974, 1021, 1022, 1787, 2105] The greatest incidence was found between the ages of seven and 14, with its peak at eight to nine years; girls were affected about twice as frequently as boys.[974, 1102, 1787, 2105] White children were affected more than twice as frequently as colored children.[1787]

Emotional factors were believed important in its pathogenesis,[1021, 1786, 2105] with the home environment more often responsible for disturbances than school life.[2105] Chorea was also more common in urban localities, areas of crowded population, and in large families.[2105] The incidence of chorea was believed to be decreasing,[974, 1787] possibly as a result of higher standards of living and improved general nutrition.

Association of Chorea and Rheumatic Fever. Chorea was the initial manifestation of rheumatic fever in 127 of 689 patients.[974] Of 88 patients observed during the initial episode of chorea, evidence of active rheumatic fever was found in 31 of the 37 patients (84 per cent) with an elevated sedimentation rate. The other 51 patients with normal sedimentation rates had marked emotional instability and no greater incidence of rheumatic fever than the same age group of the general population.[1021] Other reports gave evidence of rheumatic carditis associated with chorea as high as 38 per cent,[1022] 36.4 per cent[1787] and 47 per cent.[1102] It was felt that not all attacks of chorea are associated with rheumatic fever. Patients with a normal sedimentation rate and no other rheumatic manifestations during their initial episode of chorea probably did not have rheumatic fever, and might have similar recurrences of chorea with no evidence of rheumatic fever.[1022] The almost simultaneous occurrence of rheumatic fever with Sydenham's chorea and disseminated lupus erythematosus in a young girl, with the demonstration of both diseases at autopsy, suggested a similar pathogenesis.[103] The serum levels of the nonspecific hyaluronidase inhibitor were not elevated in Sydenham's chorea uncomplicated by other rheumatic manifestations, and correlated well with changes in blood sedimentation rate and temperature.[670]

Treatment. Walker [2106] preferred treatment in the hospital, emphasizing physical and emotional tranquillity, correction of faulty home environment, improvement of nutrition, and moderate use of such drugs as calcium, aspirin or phenobarbital. Nirvanol was considered effective by some,[1102] too toxic by others.[2106] Alphatocopherol [450] and pyridoxine [1787] also were advocated.

Rheumatoid Arthritis

(Synonyms: Chronic Infectious, Atrophic, Proliferative)

Rheumatoid arthritis, the greatest crippler among the rheumatic diseases, continues to stand as one of our most important economic and social problems. Victims of the disease are usually struck during their most productive years.[866]

The gravity of its economic impact was shown in a study of 532 patients with rheumatoid arthritis, 58 per cent of whom were unable to carry on their normal occupations because of the disease.[504]

Incidence. From a Scottish population of 40,000, a total of 1,027 new cases of rheumatism was reported during two months, of which 100 were diagnosed as rheumatoid arthritis.[1477] In 1943, of those seeking medical care in Sweden because of rheumatism, nearly one third (0.25 per cent of the total population) had rheumatoid arthritis.[336] Patients with rheumatoid arthritis make up approximately one third of admissions to most large arthritis clinics.[172, 1585] During the war, the same relative incidence prevailed at U. S. Army Hospitals (see tables 2 and 3).

The incidence of rheumatoid arthritis was greater in temperate climates than in the tropics.[341, 2000] Larsen [1175] studied the incidence of arthritis in the Hawaiian Islands in relation to the degree of "wetness" or average rainfall. On 18 plantations with a rainfall of less than 50 inches per year the incidence for rheumatoid arthritis was 61.2 per 100,000 population; on eight plantations with an annual rainfall exceeding 100 inches, the incidence was 114.5 per 100,000 population.

Clinical Features of Rheumatoid Arthritis

Age and Sex. The onset of rheumatoid arthritis is not limited to any age group and may occur from infancy to senility.[106] The disease was more common among females, with an approximate sex incidence in Great Britain of 100 males to 348 females.[504] Contrary to popular belief, however, rheumatoid arthritis did not have a predilection for young women. Statistical study showed that the risk of developing the disease increased progressively for men and single women with each five-year age group from 15 to 54; for married women, the risk increased up to the age of 35 and then remained stationary.[504]

Precipitating Factors. While the onset may be not marked by any special provocative incident, according to Cecil the majority suffered some immediately preceding strain to the physical equilibrium.[297] In a detailed study of possible precipitating factors in 100 soldiers with rheumatoid arthritis,[544] some factor which could have acted as a "trigger" was chronologically related to the onset in 42 cases. On the other hand, a study of civilian patients indicated that disease, infection and psychologic disturbances did not precede the onset of rheumatoid arthritis any more often than they preceded other diseases in a control group of patients.[504] Certain factors which have reportedly served to predispose to rheu-

matoid arthritis (heredity, body habitus, dietary imbalance, allergy, geographic environment, climate and occupation) were not considered to have contributed directly to the onset of disease.[504, 544]

Prodromal Symptoms. Prodromal symptoms of rheumatoid arthritis are usually constitutional in nature.[106, 297, 504, 1827] They may be present for months or years prior to the onset of joint symptoms,[108] following which they may persist or even become more pronounced.[336] Rarely, the prodromal period was accompanied by chills and fever simulating a pyogenic infection.[1833] A recent study suggested that the prodromal constitutional symptoms mark the actual onset of the disease, and that the so-called precipitating factors merely induce articular localization and a more recognizable phase of the morbid process.[1830]

Onset of Arthritis. The manner of onset in rheumatoid arthritis is frequently "atypical." When the early joint symptoms of 200 patients were analyzed, in only 37.5 per cent were they "typical," with insidious onset in the small joints, symmetrical distribution, and slow, centripetal progression.[488] In the remaining patients the early joint symptoms were acute in the small joints in 7 per cent, acute in the large joints in 8.5 per cent, mild and asymmetrical (usually in the hands and feet) and associated with a low sedimentation rate in 1 per cent, arthralgia only (usually of the hands) in 10 per cent, and totally uncharacteristic in 36 per cent. In 532 patients the onset of the disease was atypically febrile in 17 per cent; acute rather than insidious in 44 per cent, and monoarticular in 41 per cent.[504] A prodromal period accompanied by sweats predisposed to a febrile onset. Prodromal symptoms usually antedated a polyarticular onset.

Articular Manifestations. The first joints affected in 97 cases of peripheral rheumatoid arthritis were, in decreasing order of incidence, the knee, fingers, wrist, ankle, foot, elbow, shoulder and others.[1477] It was stated by some[504] that excessive use predisposed certain joints to preferential involvement, while others[883] noted that early joint localization was not influenced by the stress of occupation, habit (right- vs. left-handedness), or weight-bearing (upper vs. lower extremities).

After the disease had become established symmetrical joint involvement was characteristic.[106, 179, 504, 1306, 1827] It was again emphasized that the proximal interphalangeal and metacarpophalangeal joints are commonly affected, the terminal interphalangeal joints rarely.[297, 509, 1070, 1840] When the metatarsophalangeal joints are affected first and sufficiently to cause pain and tenderness, but insufficiently to produce swelling or roentgenographic changes, an erroneous diagnosis of "painful flat feet" or "foot strain" may be made.[1056] Synovial thickening may be an important physical sign of rheumatoid synovitis.[1306] This was most easily demonstrated around the knee joint, where the thickened synovia can be palpated at the insertion of the quadriceps pouch and along the femoral condyles. In reporting eight cases of opera-glass hand (chronic absorptive arthritis), Solomon and Stecher[1896] disputed the assumed rarity of this condition. They did, however, agree with the generally held concept that it represents a rather malignant variant of rheumatoid arthritis in which the severely involved joints fail to ankylose, because of partial absorption and reshaping of the articulating cartilages and epiphyseal bone.

Extra-Articular Manifestations. The generalized nature of rheumatoid arthritis is revealed not only by its constitutional symptoms but also by its many other extra-articular manifestations:

Cutaneous and Subcutaneous Manifestations. The usual skin manifestations were reviewed.[106, 108, 179, 336] In 93 patients with palmar erythema associated with various diseases, including rheumatoid arthritis, hypoalbuminemia was found somewhat more often (82 per cent) than in an unselected group of hospitalized patients without erythema (62.5 per cent).[997] Palmar erythema was also attributed to liver dysfunction.[86]

Subcutaneous nodules were reported in 12 per cent [504] to 20 per cent,[336] but in 300 patients who had been followed since 1928 the total incidence at some time during their course was above 30 per cent.[1306] An instance of multiple tender, subcutaneous cysts, simulating bursae and ganglia, was thought to be due to liquefaction of subcutaneous nodules.[1922] In contrast to their usual subcutaneous location, nodules situated in the skin were described in the fingers and toes, in the finger-pads and over the elbows.[261] These were often at the sites receiving excessive pressure in the performance of household duties and could be produced experimentally by pencil-point pressure.

Involvement of Tendon Sheaths and Palmar Fascia. Rheumatoid tenosynovitis, most commonly seen on the dorsum of the fingers, hands and wrists, also occurred about the elbows and the dorsum of the feet.[1894, 1895] The lesions were usually cystic painful swellings of varying size; they were movable and unattached to the skin but fixed to the underlying tendon structures. In contrast, the subcutaneous nodule was rarely cystic or painful, and biopsy afforded histologic differentiation. The clinical course of rheumatoidal tenosynovitis was that of the parent disease, subsiding without permanent residue during remissions of the disease and requiring no specific treatment.

Three patients with rheumatoid arthritis showed transient palmar and digital contractures, lasting a day or so and alternating from one hand to the other, thus differing from chronic Dupuytren's contractures, which have been previously described in rheumatoid arthritis.[261] The suggested mechanism was "rapidly evolving granuloma of the palmar aponeurosis."

Neuromuscular Manifestations. Although neuromuscular findings in rheumatoid arthritis may be prominent, they are frequently ignored.[1992] Muscle weakness, usually associated with atrophy, may be one of the most disabling features and, along with tremor, twitching, numbness and paresthesia, may suggest the diagnosis of a primary neurologic disorder.[108, 644, 1435] Vegetative disturbances (abnormal sweating, marked cyanosis, edematous swellings of the skin of the hands, pigmentary changes of the nails and skin, etc.) were found in 31 of 58 patients.[1992] Electromyographic studies on 34 patients with rheumatoid arthritis demonstrated an inconstant state of tension in muscles related to involved joints, whereas the muscles of normal individuals in a relaxed state showed no electrical activity.[1435] [In the experience of one of us, C. R., no muscle action potentials were detected by the electromyogram when patients with rheumatoid arthritis were in the relaxed state, but they appeared when the related joint was placed in a painful position.—Ed.] In one patient, disordered muscle functions preceded clinical evidence of articular disease. Spontaneous muscle activity was not peculiar to rheumatoid arthritis; it was found in other types of arthritis, and similar patterns were seen in poliomyelitis and infectious polyneuritis, and after nerve injuries. It was concluded that rheumatoid arthritis may directly involve the neuromuscular system, and that spontaneous muscle activity may result from lesions in the lower motor neurons.[1435]

Cardiac Manifestations. The postmortem discovery of cardiac lesions in a high percentage of patients with rheumatoid arthritis has led to extensive clinical studies of the heart. In one investigation, the results of auscultatory examinations, roentgenograms of cardiac contour, and electrocardiograms were approximately the same in 147 patients with rheumatoid arthritis as in 100 carefully

matched normal subjects.[1727] Similar conclusions were reached in two additional studies.[1253, 1707] Other investigators indicated a higher incidence of organic heart disease, in better agreement with necropsy observations, "particularly if more attention be paid to equivocal cardiac signs in patients with this disorder."[201] In one study, 16 of 45 rheumatoid patients (35.8 per cent) showed cardiac deviations from "normal," although the evidence in nine was admittedly insufficient to warrant a positive diagnosis of organic heart disease.[201] [This study relied heavily on electrocardiographic abnormalities. In only one of these 16 was a diastolic murmur recorded; in three others a systolic murmur was heard.—Ed.] X-ray evidence of cardiomegaly was found in 14 of 60 patients with rheumatoid arthritis, an incidence of 23 per cent.[553] [The inconsistent conclusions derived from these clinical inquiries into the status of the heart in patients with rheumatoid arthritis indicate a need for further study, using exact diagnostic criteria and carefully matched control subjects.—Ed.]

Pulmonary Manifestations. Pulmonary manifestations of rheumatoid arthritis, distinguishable from miliary pulmonary tuberculosis and sarcoidosis, were described in five patients.[163, 499, 1215] The pulmonary involvement was usually transient, lasting from weeks to months, with nonspecific clinical signs and characterized in roentgenograms by widespread, reticulated, mottled infiltration. Postmortem examination in two cases showed interstitial pneumonitis, with well-marked fibrinoid necrosis between the lung alveoli, similar to that described in other collagen diseases. Pathologic findings suggested an anaphylactic mechanism in the production of pulmonary lesions.

Amyloidosis. Amyloidosis was found in four of 58 autopsied cases of rheumatoid arthritis, and was diagnosed in six of 56 living patients with rheumatoid arthritis.[2083] Among the latter, the arthritis was severe in all cases and ranged in duration from two and one-half to 29 years, but was no worse or more protracted than in many cases without amyloidosis. Doubt was again expressed concerning the significance of some of the results of the Congo red test.[1313]

The amyloidosis of rheumatoid arthritis is of the secondary type and involves the kidneys most frequently; less often, the liver and spleen; and rarely, the adrenals, lymph nodes and intestines.[989] Kidneys or spleen may be involved alone. [Amyloidosis should be suspected in rheumatoid arthritis if albuminuria is marked, and if the liver and spleen are enlarged. Liver or lymph node biopsy may aid in diagnosis. The prognosis is grave in the presence of nitrogen retention.—Ed.]

Other extra-articular manifestations, such as those in the eye,[108, 481, 1891] spleen, lymph nodes, pleura and pericardium, were reviewed.[106, 336, 699] Rheumatoid arthritis accompanied by splenomegaly and leukopenia ("Felty's syndrome") was again described in several case reports.[105, 260, 535, 692, 892, 1206, 1708, 1872, 1985, 2245]

Special Features. *Effect of Hepatitis.* It is now well known that hepatitis or biliary obstruction can induce temporary, partial or complete remission of rheumatoid arthritis. Attempts to probe the mechanism by which such relief is obtained have proved futile.[710] Hepatitis was induced experimentally in two of 10 rheumatoid patients who were inoculated with serum from patients with acute infectious hepatitis.[1667] Both experienced dramatic subjective and objective improvement in their arthritis, with greatest relief when icterus was maximal. Six months later, one had relapsed partially and the other completely. When hepatitis and jaundice complicated chrysotherapy in four patients, transient improve-

ment in the arthritis was experienced by three, one of whom had a complete remission even before the onset of jaundice.[803]

Effect of Pregnancy. Several authors commented on the curious relief from rheumatoid arthritis during pregnancy and for varying periods following delivery.[97, 172, 504, 1150] Marked improvement or complete remission occurred in most of 150 patients.[848] Of those improved, relief was noted in 90 per cent during the first trimester and in 10 per cent during the second. Rheumatoid arthritis rarely had its onset during pregnancy. Patients whose rheumatoid arthritis was relieved once during pregnancy were usually relieved by subsequent pregnancies; those not relieved initially were usually not relieved by subsequent pregnancies. Relief of joint symptoms ended most often within one to six weeks postpartum; in some, relief persisted for eight to 12 weeks; in a few, four to 24 months. Postpartum return of joint symptoms was not influenced by duration of bed-rest or of lactation, or by the approach of the first postpartum menses. The mechanism by which relief is induced by pregnancy remains unsolved and no elucidative data appeared. Remissions in pregnancy and jaundice were not associated with changes in the serum lysolecithin level.[1150]

There was no conclusive evidence that pregnancy predisposed a patient to rheumatoid arthritis.[504] The proportion of patients developing rheumatoid arthritis within one year after pregnancy (19 per cent) seemed rather large when compared with a control group (11 per cent), but the difference was not greater than could have arisen by chance.

Pathologic Characteristics of Rheumatoid Arthritis

The pathologic changes in rheumatoid arthritis are widespread, involving a variety of organs and tissues, predominantly the connective tissues.[107] Often the histopathology is relatively specific, characterized by both degeneration and proliferation.[108] Some [198, 1644] referred to these changes as those of necrobiosis, "what goes on in a part when a degenerative necrotic focus is opposed by a vital reactionary process of repair and regeneration." [2137] These alterations were seen best in the subcutaneous nodule but were also observed in the sclera, pleura, heart and pericardium, peritoneum, splenic capsule, larynx and other organs, thereby establishing the systemic nature of rheumatoid arthritis.[108, 263, 729, 1644]

Subcutaneous Nodules. Subcutaneous nodules of rheumatoid arthritis were characterized by a granulomatous reaction containing necrobiotic foci.[2137] Each of these foci had three distinct zones: (1) a central area of necrosis; (2) an intermediate zone of fibroblasts in palisade arrangement, and (3) a peripheral zone of cellular infiltration (largely lymphocytes and plasma cells) into the surrounding connective tissue.[1306] Some nodules contained giant cells as well as lipid substance, including crystalline cholesterol.[1644] The presence of the latter indicated secondary infiltration into the necrotic foci, and not a separate entity.[930]

Biopsy of nodules was helpful in differentiating rheumatoid arthritis from other rheumatic diseases. Bauer and Stall [1306] contrasted the histology of rheumatic and rheumatoid nodules and pointed out the tendency of the latter to persist because of residual postdegenerative scarring. Despite a close histologic resemblance between rheumatoid nodules and granuloma annulare, there were certain minor differences.[198] [It was emphasized that histologic resemblance does not imply identical etiology.—Ed.]

Joints. Pathologic alterations in the joints were described.[39, 297, 317, 600] The primary lesion was in the synovial membrane, which became thickened by fibrosis

and inflammatory cellular infiltration. Contrary to other opinion, Flynn considered collections of lymphocytes not specific for rheumatoid arthritis, as they were found in other articular diseases.[317]

Tendons. Rheumatoid alterations in tendons may simulate those of the synovial membrane, showing a similar combination of fibrosis, round cell infiltration and necrosis. In advanced disease the tendon may be grossly thickened and nodular.[1049] If transverse fibrous bands in the tendon sheaths soften and disintegrate the patient experiences little disability; but if the transverse bands remain intact the thickened tendons become jammed, resulting in interference with function. Small nodules in flexor tendons of the hands may cause snapping fingers, while large nodules may become impacted between two transverse bands, causing loss of all active flexion.

Bones. The marrow spaces beneath the subchondral plate are normally occupied by fibro-fatty tissue. In severe rheumatoid arthritis, granulation tissue occupies these spaces, and its proliferation destroys osseous trabeculae and the subchondral plate. Hence, the articular cartilage may be attacked on one side by pannus and on the other by granulation tissue from the marrow spaces.[317]

Neuromuscular System. Isolated and distinct inflammatory reactions in the connective tissue sheaths of peripheral nerves, similar to those described previously (see Ninth Rheumatism Review) were found in about 70 per cent of 47 cases studied at necropsy.[1434, 1435] Occasionally, these foci were nodular and had poorly defined acellular centers resembling collagen. In addition, parenchymatous alterations were seen, consisting of scattered foci of degeneration of axons and myelin sheaths, with retrograde degeneration in the corresponding nerve cell bodies of the anterior horns and, less commonly, in a few of the posterior root ganglion cells. Studies of the sympathetic chain in 19 cases disclosed cellular reactions within the ganglia, along the connecting chains, or as lymphoid infiltrations in the neighboring fat. While some of these may have been composed of modified glial elements, other foci were composed of lymphocytes and plasma cells, and were often perivascular.[1534] The lesions in the peripheral nerves were not specific, since similar nerve changes were observed in dermatomyositis, lupus erythematosus and rheumatic fever.[1534, 1535] The histologic changes in the spinal cord resembled those produced by aging, but they occurred at a much younger age than in spinal cords obtained from patients with no history of neurologic disease. There was no relationship between the degree of such change and the severity, state of activity or duration of the rheumatoid arthritis.

Histologic studies of skeletal muscle in patients with rheumatoid arthritis confirmed the presence of paravascular, focal collections of lymphocytes and plasma cells in the connective tissue sheaths. Their incidence varied from 50 per cent [108] to nearly 100 per cent (*26* of *27* patients).[1950] The lesions were widely disseminated and were found in muscles remote from affected joints,[424] in extra-ocular muscles and in the diaphragm.[1434] There was no constant relationship between the presence of these inflammatory foci and muscle atrophy,[424, 1434] nor was there any relationship with the severity and state of activity of the disease.[929, 1434] In only one study was the incidence of positive muscle biopsies proportional to the duration of the disease.[424]

While these muscle lesions were considered specific by a few,[1950] such an opinion was not shared by most workers, who observed similar lesions in normal controls and in patients with a variety of diseases other than rheumatoid arthritis.[313, 424, 929, 1350, 1434, 1496, 1881]

[Despite their lack of specificity, histologic studies of the neuromuscular system in rheumatoid arthritis furnish additional evidence of the widespread nature of the disease. Furthermore, it seems likely that these pathologic observations at least partially account for many of the neuromuscular signs and symptoms so prominent in rheumatoid arthritis.—Ed.]

Cardiovascular System. Considerable interest continued in the pathology of the heart in rheumatoid arthritis. Of 66 autopsied cases, definite rheumatic lesions were

described in *26*, with inconclusive, probably rheumatic lesions in an additional nine.[689] It was again observed that the lesions were less diffuse and less severe than those usually seen in rheumatic heart disease. In two patients, a granulomatous zone of interstitial collagenous necrosis, similar to that which occurs in rheumatoid nodules, was seen in the endocardium; and in another, the pericardium showed necrotic collagenous nodules. In an autopsied series of *27* cases of rheumatoid arthritis, one showed necrobiotic rheumatoid granulomata in the aortic ring and fibrinous pericarditis, resembling the synovitis present in the same patient.[263] Rheumatoid granulomata, identical with those of subcutaneous nodules, were also seen in the tricuspid valve and in the myocardium of the right atrium.[729]

Of 45 autopsied cases of rheumatoid arthritis, Bauer and Clark described pericarditis in 44 per cent, only one-half of which were associated with myocardial infarction or alterations suggesting rheumatic fever.[108] Twenty per cent had gross valvular disease; mitral stenosis was present in 14 per cent, but in only one case could a definite diagnosis of rheumatic heart disease be made. Of great interest were six cases showing an unusual focal myocarditis and three with an unidentified aortitis, one of which showed aortic valvulitis with pannus formation. These lesions differed from those seen in rheumatic fever and syphilis and were thought to be manifestations of rheumatoid arthritis.[107] In two cases, the pericardium showed nodules indistinguishable from subcutaneous nodules of rheumatoid arthritis.

[It appears likely that certain alterations of the heart, especially those showing the characteristic histopathology of rheumatoid nodules, are additional systemic manifestations of rheumatoid arthritis. Previous studies had disclosed a high incidence of "rheumatic heart disease" in patients with rheumatoid arthritis (Ninth Rheumatism Review). The more recent observations indicate that a second group of lesions, relatively specific for rheumatoid arthritis, may also be found.—Ed.]

Laboratory Data in Rheumatoid Arthritis

Blood Counts and Erythrocyte Sedimentation Rates. These were again reviewed.[297, 335, 686, 689, 1827, 1953] It was generally agreed that the sedimentation rate is the most reliable laboratory gauge of the activity of rheumatoid arthritis. Attempts to relate hyaluronic acid to the increased sedimentation rate were unsuccessful.[2244]

Serum Proteins. Electrophoretic measurements in 46 patients revealed a marked decrease in albumin, a moderate increase in beta globulin, and a marked increase in alpha globulin, gamma globulin, and fibrinogen fractions.[1740] Similar results were obtained by others.[1998, 2118] In individual cases the return of the Tiselius pattern toward normal coincided with clinical improvement.[488, 1740] Differences from the patterns obtained in patients with rheumatic fever were noted.[1740, 1998] [These studies not only confirm but also amplify previous results based on chemical fractionation. The electrophoretic method reveals abnormalities in many situations where the customary Howe fractionation yields normal values. Further studies, particularly those susceptible to statistical analysis and suitable for correlation of laboratory results with clinical findings, should be of interest. No specificity has been established for the changes observed in rheumatoid arthritis.—Ed.]

Work continued with tests presumably dependent on alterations of serum proteins. Plasma viscosity was measured by conventional methods as well as by a simplified method.[2219] It was agreed that the plasma viscosity increases with increasing concentration of plasma proteins, and that the plasma viscosity test is likely to be more dependable in patients with rheumatoid arthritis of great severity and long duration.[407, 984, 1617, 2219] [It apparently offers little of diagnostic or prognostic value since, like the erythrocyte sedimentation rate, it is nonspecific. In some instances, however, it may

indicate active disease when the sedimentation rate is normal.—Ed.] Further use of the colloidal gold test largely confirmed previous work.[2003] The Weltmann reaction was again reviewed.[1284]

Synovial Fluid. In an analysis of 1,000 synovial effusions due to various causes, including rheumatoid arthritis, the significant pathologic findings in the rheumatoid fluids (exact number not stated) were abnormal gross appearance, increase in leukocytes and percentage of polymorphonuclear cells, elevation in protein concentration, increase in the sugar differential between joint fluid and serum, and alterations in the mucin.[1716] The degree of abnormality increased with the severity of the disease, although the degree of change was not necessarily proportional. Examination of joint fluid was helpful in diagnosis and especially useful in the differentiation between rheumatoid arthritis and traumatic arthritis, degenerative joint disease or Charcot's joints; in the latter group, inflammation was minimal and synovial fluids showed correspondingly little deviation from normal. [Further details are given in a recent publication (1952) by the same authors. Rheumatoid joint fluids ranged from normally clear in mild cases to frankly turbid in advanced disease. Clot formation was frequent. In mild cases, the white cell count was as low as 600 per cubic millimeter, but the average was 14,000 and the recorded high 66,000 (normal range, 13 to 180). A percentage of polymorphonuclear cells as low as 5 was noted in mild rheumatoid disease; the average was 65 per cent and the high 96 per cent (normal, 0 to 25 per cent). Protein concentrations varied between 3.0 gm. and 8.9 gm. per 100 c.c., average 4.9 gm. per cent (normal, 1.3 to 2.1 gm. per cent). The sugar content of joint fluid was 0 to 88 mg. per cent less than that of serum, with an average difference of 31 mg. per cent (normal difference, less than 10 mg. per cent). The highest figures were obtained in patients with rheumatoid arthritis of long duration. Alteration in joint fluid mucin was best shown by gross inspection of the precipitate obtained by adding acetic acid to the joint fluid to a final concentration of 1 per cent. The precipitate from normal fluid was a tough, ropy clump, with clear surrounding solution, whereas in rheumatoid arthritis the mucin usually precipitated into a soft clump with a cloudy solution; in severe cases there was no clump, and only a cloudy solution resulted.—Ed.] Electrophoretic patterns of synovial fluid proteins showed occasional alterations in the same directions as those of serum, because of the increased permeability of the synovial membrane.[1714] The latter often demonstrated a differential permeability to individual protein fractions.[1996]

It is of particular interest that an increased amount of hyaluronate with a low degree of polymerization was found in rheumatoid joint fluids. The degree of polymerization varied with the activity of the disease, becoming less complete as the disease became more active. This was believed to be due to an increased production of incompletely polymerized hyaluronate rather than to an excessive breakdown of hyaluronic acid. On the assumption that these alterations parallel changes in the smaller connective tissue spaces throughout the body, it was suggested that a primary fault in rheumatoid arthritis is in connective tissue cells, which are unable to complete the normal synthesis and polymerization of hyaluronic acid (Ragan and Meyer[1630]).

Roentgenograms. Well recognized roentgenographic abnormalities were reviewed.[297, 654, 1540, 1957] It was again emphasized that x-ray findings in peripheral rheumatoid arthritis are not specific.[1540] Osteoporosis, often generalized, is the first radiographic change, and its prompt recognition may assist early diagnosis.[1958] Recalcification may take place when the disease becomes quiescent, although the bones do not usually regain their normal appearance.[1812]

Serologic Tests. Since most workers[317, 586, 2113, 2115] agreed that the various streptococcal agglutinations, as well as other streptococcal antibody determinations, lacked specificity and sensitivity, considerable interest was aroused when

Rose, Ragan, Pearce and Lipman [1717] proposed a serologic test for which they claimed good specificity and high correlation with rheumatoid activity. These workers discovered that the sera of patients with active rheumatoid arthritis agglutinated sheep erythrocytes sensitized with anti-sheep hemolysin in a much higher dilution than it did normal sheep cells. The test consisted in a comparison of the titers at which sensitized and normal sheep cells were agglutinated; the resulting "differential titer" was "never lower than 16 and usually considerably higher" in patients with active rheumatoid arthritis, whereas it was less than 16 in most other conditions. In confirmatory studies, some investigators were in agreement,[84, 233, 441, 596, 1997] but others had reservations about the specificity and significance of the test. Mild yet active cases gave differential titers below 16 in as many as 57 per cent [1956] to 85 per cent [983] of the cases studied. The differential titer seemed to parallel activity [983] but not the clinical response to corticotropin.[1997] Others workers felt that the test failed to contribute to the diagnosis of rheumatoid arthritis.[1404]

Because some workers frequently encountered low differential titers in active rheumatoid arthritis, and occasional high titers in other illnesses, attempts were made to modify the procedure to obtain greater specificity. The agglutinating factor in the patient's serum was not identical with the heterophil antibody [84, 983] and was probably a globulin.[1717] (See additional discussion under Etiology and Pathogenesis.) Since the serum factor was not removed by materials which absorbed heterophil or infectious mononucleosis antibodies, elimination of the latter antibodies by absorption with normal, unsensitized sheep cells was undertaken. Methods utilizing this procedure claimed 90 per cent positive results in active rheumatoid arthritis, and negative results in inactive rheumatoid arthritis and in other diseases.[840, 1999] These findings were not confirmed by all.[1574] [It is evident that minor modifications of technic have a major influence on results, and that true specificity has yet to be established.—Ed.]

Spinal Fluid. Abnormalities were reported in the spinal fluid in 46.8 per cent of 141 patients with rheumatoid arthritis. As in previous studies, these were chiefly alterations in protein content.[1992]

Etiology and Pathogenesis

Factor of Infection. While evidence mounted against the theory of "focal infection,"[391, 504, 600] interest continued in the possible rôle of streptococci in the etiology of rheumatoid arthritis.[2015] Several investigators reëxamined various technics for the detection of agglutinating antibodies against Group A hemolytic streptococci.[299, 1024, 2187] Positive results were observed in 50 per cent to 80 per cent of adult subjects with rheumatoid arthritis, while a high titer was rare among normal controls. [Differences in technic may account for wide differences in results.—Ed.] Few patients with diseases other than rheumatoid arthritis were found to possess this agglutinating property. Wallis found that rheumatoid sera, in contrast to normal sera, agglutinated suspensions of fine collodion particles.[2116] Because of this and the presence of feeble agglutinins for streptococci in normal individuals, it was postulated that the increased ability was due to a nonspecific enhancement of the action of agglutinins normally present, and not to an increase in agglutinins. [Not all agreed with this explanation of an interesting phenomenon. However, the apparent increase in streptococcal agglutination may be a nonspecific reaction; the significance of this phenomenon in the etiology of rheumatoid arthritis is still unknown.—Ed.]

Similar doubts were expressed regarding the specificity of precipitin reactions in rheumatoid arthritis.[2113] Rheumatoid sera tended to precipitate in saline controls, especially after centrifugation, and, in contrast to normal sera, agglutinated fine collodion particles [2115] and the somatic carbohydrate of the pneumococcus.[2114] Other antistreptococcal antibodies were also examined. The mean titers for antistreptolysin and streptococcal antihyaluronidase were nearly identical with those of normal subjects.[802] [Some workers who had previously reported elevation of antistreptolysin titers in early cases of rheumatoid arthritis later believed this information was based on cases of adult rheumatic fever which had been misdiagnosed. The low antibody titers against these streptococcal products do not lend support to the hemolytic streptococcus as the etiologic factor in rheumatoid arthritis.—Ed.]

Studies concerning the rôle of pleuropneumonia-like organisms in joint disease continued.[235, 431] Despite their presence in the joint fluid of two patients with arthritis (associated with disease of the genitourinary tract in both cases), the evidence for the pathogenicity of pleuropneumonia-like organisms in joint disease and particularly in rheumatoid arthritis remained inconclusive.[431]

Factor of Hypersensitivity. Rheumatoid arthritis was regarded by some as related to the hypersensitive state (discussed under The Collagen Diseases), but further definitive observations were not reported. A few workers observed improvement in rheumatoid arthritis patients after use of various measures that are sometimes effective in allergic states, and concluded that allergy either was a component in the production of the disease [2253] or was wholly responsible for the disease.[1706]

The increase in gamma globulin demonstrated by electrophoretic and immunologic measurements was assumed to reflect antibody production, a significant factor in some concepts of pathogenesis of the rheumatoid state.[2116] [However, the identity of the responsible antigen or antigens is not known. In more recent studies (Olhagen, 1952), the removal of specific streptococcus agglutinins did not alter the electrophoretic pattern of rheumatoid arthritis serum, and there was no apparent correlation between gamma globulin concentration in plasma and the titers of streptococcus agglutinins, of antistreptolysins or of differential agglutinins of sheep red cells.—Ed.] The substance responsible for the agglutination of sensitized sheep cells was localized in the globulin fraction of the serum,[1717] but was not directly associated with streptococcus agglutinins or with factors responsible for alterations in erythrocyte sedimentation rate.[1574] Immunologic studies suggested that the chief activity of this serum factor in active rheumatoid arthritis may be one of marked augmentation of the agglutinating ability encountered in the sera of many normal persons. It undoubtedly represented an abnormal protein somehow related to rheumatoid activity, but appeared to be neither an antibody nor specifically and etiologically related to the rheumatoid process.[1574] It was shown that rheumatoid sera contained a factor which caused significant precipitation with a saline extract of human connective tissues.[1171] The latter did not seem to act as antigens, since the reaction fixed complement only slightly or not at all. [The nature of this reaction is as little understood as that of the differential agglutination of sensitized sheep cells by rheumatoid sera.—Ed.]

Wallis theorized that the antigen responsible for excessive antibody production in rheumatoid arthritis was a by-product of the synovial cell.[2119] He suggested that the pathogenesis of rheumatoid arthritis is based on the effects of fixation of antibodies by tissues in the smooth muscle walls of arterioles.[2117, 2118, 2119, 2120] As a result of this antibody fixation, a metabolite of arteriolar smooth muscle action interferes with synthesis of hyaluronic acid by synovial cells, "leading to the production of two abnormal substances, one an irritant responsible for the patient's symptoms and the other an antigen, which by arousing antibodies completes a vicious circle whereby the

disease process perpetuates itself." External factors lead to a "naturally high vascular tone" which fatigues vasoconstrictor muscles, discharges metabolites and thereby initiates the cycle. [This hypothesis appears complicated and does not readily suggest avenues by which it may be tested experimentally.—Ed.]

Factor of Altered Metabolism. A majority of 64 patients with rheumatoid arthritis showed a slower fall in the blood sugar level after the intravenous injection of glucose than did normal subjects.[565] Use of the intravenous route excluded gastrointestinal dysfunction as an explanation for this phenomenon. Since no such delay occurred in 19 patients convalescing from severe poliomyelitis, despite equivalent or greater muscle atrophy, diminution of peripheral glycogen depots did not explain the alteration found in rheumatoid arthritis. The abnormal glucose tolerance in rheumatoid arthritis could be attributed to an altered threshold of the hepatic homeostatic regulation of the blood sugar. Whether such a derangement emanated from extrahepatic hormonal influences could not be determined on the basis of this study. In an analysis of 1,008 patients with rheumatoid arthritis and 756 with diabetes mellitus, the coincident occurrence of these two diseases in the same person corresponded to the average incidence of both diseases in the general population.[962]

Continued interest was shown in the possibility of an intrinsic disturbance of protein metabolism in rheumatoid arthritis. Eight rheumatoid patients and two normal individuals were the subjects of balance studies measuring the degree of protein retention following change from a low-protein to a high-protein intake. The pattern of the protein retention was not related to the severity or the duration of the arthritis. Greater than normal retention occurred in those patients who were most markedly underweight.[1701] Preliminary results of determinations of urinary excretion and plasma levels of individual amino acids showed no striking deviation from normal values in patients with rheumatoid arthritis.[199, 221]

Factor of Altered Nutrition. There was no correlation between the urinary excretion of vitamin B components and the duration or severity of rheumatoid arthritis.[115] Fasting and saturation tests on 40 patients showed that recovery of thiamin, riboflavin and nicotinic acid was essentially the same as in controls. It was again emphasized that no essential food factor or diet is involved in the causation of rheumatoid arthritis.[1699, 2067]

Factor of Endocrine Imbalance. The profound effect of corticotropin and cortisone in the treatment of rheumatoid arthritis naturally stimulated interest in possible endocrine or hormone-related factors in the pathogenesis of the disease. [This subject, including tests of adrenocortical function in rheumatoid arthritis, is reviewed in the section on The Adrenal Cortex and Rheumatic Diseases.—Ed.] In nine of 10 autopsied cases of active rheumatoid arthritis, and in one of three cases of lupus erythematosus disseminatus, identical abnormalities of the pituitary glands were observed.[1546] These consisted of a selective degranulation of the mucoid cells (basophils, cyanophils) similar to that seen in Addison's disease but not found among the 200 controls. These alterations, allegedly specific, were considered to be secondary to dysfunction of the adrenal gland. [These observations were made with special staining technics which require new definitions and concepts of pituitary cytology. Efforts to confirm this work should be most valuable.—Ed.]

An abnormality in metabolism of cortisone in affected tissues in rheumatoid arthritis rather than a deficient adrenal production of this hormone was suggested by the high dosage level required for relief of symptoms, as well as by the absence of recognizable evidences of adrenal insufficiency. Being unable to test this hypothesis directly, Sommerville, Marrian, Duthie and Sinclair [1888] investigated the metabolism of progesterone. The percentage recovery of intramuscularly injected progesterone in the urine as pregnanediol was higher in all of 13 patients with rheumatoid arthritis than in any of 10 normal subjects. The values ranged from 9.3 to 16.0 per cent in normals, as opposed to 19.0 to 36.4 per cent in the arthritics. [The authors recognized the need for quantitative studies on the conversion of administered progesterone in a wide variety of clinical conditions. More recently Dobriner, using laborious isolation methods, has found the excretion of steroid hormone metabolites to be consistently at a low normal level in five patients with rheumatoid arthritis. In addition, four of the five patients excreted a steroid, 17-hydroxy pregnenolone, that has been encountered only in subjects with manifest adrenal dysfunction. There is obvious need for further work to elucidate the significance of these observations and to establish their specificity for rheumatoid arthritis. Thus far, no abnormality in metabolism of cortisone by patients with rheumatoid arthritis has been demonstrated.—Ed.]

Factor of Trauma. In only one of 1,669 patients with rheumatoid arthritis was trauma considered to be a direct causal factor.[1012] However, joint injury may serve as a precipitating factor. In 100 soldiers with rheumatoid arthritis, direct trauma to a joint acted as the "trigger" factor in 5 per cent.[544] Repeated microtrauma may play a more significant rôle, because joints of the lower extremities were first involved in 82 of the 100 soldiers. Various traumatic procedures applied over the olecranon process in 39 patients with rheumatoid arthritis failed to induce subcutaneous nodules in a single patient.[1784]

Factor of Autonomic Imbalance. Vasomotor adaptability was studied in 24 patients with rheumatoid arthritis by recording cutaneous temperatures of the extremities in normal, cold and hot environments. No constant defect in peripheral circulatory adaptability was found. However, the majority demonstrated intolerance to cold, sometimes associated with a very slow decrease of cutaneous temperature, presumably due to abnormally sluggish and incomplete vasoconstriction of hands and feet. Cutaneous vasodilation was also frequently slow and irregular in response to warm environmental temperature.[1301] Increased sensitivity to methacholine was observed commonly in patients with rheumatoid arthritis and in patients with adrenocortical insufficiency, but rarely in patients with other diseases or in normal subjects.[1552] It was not determined whether the difference in responsiveness was related to function of the autonomic nervous system or of the adrenal cortex.

Factor of Psychogenesis. Some workers viewed rheumatoid arthritis as a psychosomatic syndrome.[321, 995] Environmental factors (finances, employment, housing, diet, special wartime problems, psychologic problems) were studied in 100 patients, and abnormalities in the psychologic environment were found in 74 per cent. Such psychogenic precipitating factors as shock, worry and grief were temporally related to initial onset in 10 of 13 patients.[64] In other studies, psychologic factors did not precede the onset of rheumatoid arthritis more often than they preceded other diseases.[804]

A consistent personality pattern was found in each of several patients with rheumatoid arthritis. Observable in all were "extreme degrees of emotional insecurity and dependence, marked feelings of inadequacy and inferiority, plus a tendency toward a high degree of emotional isolation." A similar personality pattern was seen in such psychosomatic disorders as obesity, Raynaud's disease and ulcerative colitis.[1255] Some investigators felt that rheumatoid arthritis might be precipitated by "muscle spasm and increased muscle tonus."[995] The latter was presumed to be the somatic expression of an unconscious conflict between "chronic hostile aggressive impulses and the defense against them."

Gottschalk and his collaborators[687] applied a psychosomatic method for investigating the neuromuscular system to patients with rheumatoid arthritis. Preliminary findings reflected psychologic tensions and conflicts through variations in the tracings of the electromyogram, although patients with other types of illness had similar tracings. During psychoanalytic therapy, the muscular tension of rheumatoid arthritics was reduced. In another group the handwriting was studied by means of the graphodyn, an instrument which measures impairment of expressive muscular performance.[686] No quantitative difference was found between the tracings of patients with rheumatoid arthritis and other patients with symptomatic disease used as controls.

Conclusions Regarding Etiology. It is apparent that the cause of rheumatoid arthritis remains unknown. Nevertheless, the foregoing studies should provide stimulus for new investigations which will help to establish its etiology and pathogenesis.

Relationship Between Rheumatoid Arthritis and Other Diseases

Other "Collagen Diseases." Morphologic and clinical similarities suggesting a close relationship between rheumatoid arthritis and rheumatic fever, lupus erythematosus disseminatus, periarteritis nodosa, dermatomyositis and scleroderma[109, 317] are discussed in the section on "Collagen Diseases." Most helpful in the differentiation of rheumatoid arthritis from the other collagen or "connective tissue" diseases were the progressiveness and severity of the arthritis, the presence of ocular disease (scleromalacia perforans, episcleritis or, more commonly, uveitis), the usual absence of renal abnormalities, and the relatively specific pathologic alterations in the subcutaneous nodule.[109, 1954]

Rheumatic Fever. It was again suggested that rheumatoid arthritis and rheumatic fever are closely related diseases, perhaps even the same basic disease with different predominating clinical characteristics.[317, 1068, 1707, 1883, 1951] The similarities of early symptomatology, particularly in adults, the frequently observed transition of presumed rheumatic fever into chronic rheumatoid arthritis, and similar morbid pathology in certain organs (especially the heart) prompted these considerations (see Pathology; Cardiovascular System).

A series was reported consisting of 39 adults with "chronic rheumatic fever" in whom the early clinical course "simulated that of typical rheumatoid arthritis."[187] Early differentiation in these cases could be made only by serologic means "or by observation of the patient for a prolonged period of time—preferably for more than seven months." At the time of follow-up examination, two to 14 years after the onset, one patient had a fixed temporomandibular joint but none showed the usual deformities of rheumatoid arthritis. In a comparative study of a group of 252 soldiers with rheumatic fever, and a group of 33 soldiers with an acute febrile onset of "atypical" rheumatoid arthritis, Engelman emphasized certain salient differential

features which may be helpful in diagnosis.[808] Seventy-four per cent of the rheumatic fever patients had an antecedent sore throat or respiratory infection (within 28 days of onset), while only 9 per cent of the rheumatoid arthritic patients gave a like history. Although many rheumatic fever patients continued to experience joint pains for several months, their joint effusions usually disappeared within a few days and always within 18 days, provided adequate doses of salicylates were administered. Salicylates had no like effect upon rheumatoid effusions, which persisted for five weeks to several months in 91 per cent of the rheumatoid patients. The erythrocyte sedimentation rate was elevated for an average of 10 weeks in the rheumatic fever patients and for 25 weeks in the rheumatoid arthritis patients. Absence of carditis was not considered a criterion for differentiation, as carditis was not detectable in a significant number of adult patients with rheumatic fever. Residual joint deformities occurred in none of the rheumatic fever patients, but were observed in 63 per cent of those with rheumatoid arthritis.

[It is emphasized that in none of the above studies was rheumatoid arthritis seen as a residue of or secondary to rheumatic fever. Similar conclusions were reached in a recent follow-up study of 215 veterans who had had rheumatic fever 3.9 to 8.2 years (average, 5.7 years) previously. Despite frequent difficulties in early diagnosis, rheumatoid arthritis and rheumatic fever should be regarded as specific entities until such time as a common pathogenesis can be established. Therapeutic and prognostic implications make mandatory every effort toward clinical differentiation.—Ed.]

Gonorrhea. During World War II, many patients with chronic arthritis following acute gonococcal infection were misdiagnosed as having "gonococcal arthritis resistant to penicillin and/or sulfonamides."[852] Most of these patients were later shown to have rheumatoid arthritis, not only by their history (subacute or insidious onset of arthritis, absence of chill) and physical findings (low-grade fever, symmetrical and multiple joint involvement), but also by the chronicity and progressiveness of the arthritis, the therapeutic ineffectiveness of penicillin and sulfonamides, the character of the synovial fluids and, in some cases, by articular biopsies. It was pointed out that rheumatoid arthritis can be precipitated or reactivated by gonorrheal infection as well as by any other acute infection.[852] [So-called "postgonorrheal rheumatoid arthritis" is neither grafted on nor evolved from a subsiding acute gonorrheal arthritis; it represents simply rheumatoid arthritis, precipitated or aggravated by acute genital (not articular) gonorrhea. These conclusions have been confirmed in additional studies.—Ed.]

Juvenile Rheumatoid Arthritis

Juvenile rheumatoid arthritis was previously divided into two types, each having a separate and unknown etiology: polyarthritis associated with severe systemic manifestations, including lymphadenopathy, splenomegaly, anemia, and sometimes adhesive pericarditis or other visceral lesions (Still's disease); and rheumatoid arthritis unaccompanied by systemic manifestations. Since the two are indistinguishable pathologically, it is now generally agreed that there is no justification for such a division.[252, 358, 481, 1166, 1229, 1568] Gradations between the two types are often seen, and systemic manifestations are known to be part of rheumatoid disease. (See General Clinical Data and Pathology.)

Juvenile rheumatoid arthritis is an uncommon disease; there were only 16 cases among 78,000 admissions to a children's hospital, an incidence of only 0.02 per cent.[1237] Many of the distinguishing features are derived from the tendency of children to show more severe systemic symptoms and signs, even spiking fever up to 105° F.[1445] and leukocytosis. Of 56 patients, lymphadenopathy occurred in 60 per cent, splenomegaly in 30 per cent, and hepatomegaly in 23 per cent.[358] Also observed was a widespread

rash, usually urticarial or maculopapular, rarely erythematous or petechial.[1445, 1775] Other characteristic features arise from rheumatoid involvement of the epiphysis, with resulting interference with growth, as seen in short, stubby fingers, a receding jaw and shortened extremities.[358, 506, 1229] The appearance of dwarfism was not unusual in patients who had reached maturity. Commonly encountered were pain and restricted motion in the cervical spine, where fusion of two or more vertebrae was often seen by x-ray; involvement of the remainder of the spine and of the sacroiliac joints was rare.[651, 1229]

In some children the early clinical course necessitated prolonged observation to differentiate between juvenile rheumatoid arthritis and rheumatic fever.[358, 1229] Occasionally a monarticular onset simulated tuberculous arthritis.[1229, 1868] Functional recovery, permitting resumption of daily activities, occurred in 75 per cent.[1229] Contrary to earlier reports, juvenile rheumatoid arthritis did not terminate with puberty.[358, 1229]

Treatment of Rheumatoid Arthritis

In a chronic disease of unknown cause, such as rheumatoid arthritis, whose natural course is often characterized by unpredictable fluctuations in activity, it is extremely difficult to evaluate the results of any form of treatment.[106] However, not all the confusion arising from conflicting therapeutic reports can be blamed on the inherent vagrancy of rheumatoid arthritis—much of it may be attributed to lack of standard criteria and statement of improvement. Several attempts have been made to establish some uniformity in recording results of therapy.[1832, 1938, 1943] In 1949 a committee of the New York Rheumatism Association proposed a uniform system for appraising therapeutic results in rheumatoid arthritis,[1948] and the criteria offered were later adopted by the American Rheumatism Association (tables 5, 6, 7). The method is based entirely on objective information and involves first a classification of patients at the beginning of therapy as to (1) stage of the disease, (2) presence of rheumatoid activity, and (3) degree (class) of functional impairment. The response to treatment is evaluated

Table V

Classification of Rheumatoid Progression

Stage	Roentgenologic Signs	Muscle Atrophy	Extra-Articular Lesions (Nodules Teno-vaginitis)	Joint Deformity	Ankylosis
I	Osteoporosis (sometimes no destructive changes)	0	0	0	0
II	Osteoporosis (slight cartilage or subchondral bone destruction may be present)	Adjacent	May be present	0	0
III	Osteoporosis (cartilage destruction, bone destruction)	Extensive	May be present	Subluxation, ulnar deviation and/or hyperextension	0
IV	Same as III with bony ankylosis	Extensive	May be present	Same as III	Fibrous or bony ankylosis

TABLE VI

Classification of Functional Capacity

Class	
I	Complete Ability to carry on all usual duties without handicaps
II	Adequate for normal activities Despite handicap of discomfort or limited motion at one or more joints
III	Limited Only to little or none of duties of usual occupation or self care
IV	Incapacitated, largely or wholly Bedridden or confined to wheelchair; little or no self care

on the basis of changes in rheumatoid activity and functional impairment, the stage of the disease not being considered, as it rarely improves. [Example: Before treatment a patient may be in Stage III, active, Class IV, and after therapy may still be in Stage III, yet show Grade II improvement of rheumatoid activity and Class II functional capacity.—Ed.]

TABLE VII

Response of Rheumatoid Activity to Therapy

Grade	Systemic Signs	Signs of Joint Inflammation	Signs of Extra-Articular Activity	Remaining Impairment of Joint Mobility	Articular Deformity	Erythrocyte Sedimentation Rate	Roentgenologic Signs
I Complete remission	0*	0*	0*	Due only to irreversible changes	Due only to irreversible changes	0*	No progression
II Major improvement	Elevated erythrocyte sedimentation rate and/or vasomotor imbalance permissible	Only minimal* residual joint swelling (no new sites)	Minimum* (no new sites)	Only consistent with minimal residual activity	Due only to irreversible changes	May be elevated	No progression
III Minor improvement	Decreased*	Only partially* resolved (no new sites)	Decreased* (no new sites)	In relation to residual inflammation	May be present	May be elevated	No progression
IV No improvement	Undiminished*	Same* or worse	Same or new sites or exacerbation*	Same, better or worse	Present or not	Any rate	Changes indicative of progression

* Indicates criteria required to be present.

Cortisone and Corticotropin in Rheumatoid Arthritis

Even the most secluded of medical hermits are now familiar with the dramatic effects of cortisone (17-hydroxy-11-dehydrocorticosterone; Kendall's Compound E; Reichstein's Compound F_a) and corticotropin (pituitary adrenocorticotropic hormone; ACTH) on rheumatoid arthritis. The discovery by Hench, Kendall, Slocumb and Polley that these hormones can rapidly ameliorate the clinical, bio-

chemical and histologic manifestations of several rheumatic diseases constitutes the greatest single advance made in the field of arthritis—as attested by the award of the 1950 Nobel Prize for Medicine and Physiology to Hench, Kendall and Reichstein. The discovery caused physicians to consider the subject of rheumatoid arthritis with greater propensity, provided new concepts and tools for research, and gave promise of a more effective method of treatment. Since the discovery, much progress has been made in determining the utility and limitations of the hormones, and it now appears that they may be employed, at least in a restricted way, as practical therapeutic agents. But much more remains to be learned about them, about their mode of action, indications, hazards and optimal methods of administration. To paraphrase Hench,[850] the discovery has not been the beginning of the end of the problem of rheumatoid arthritis, but perhaps may mark the end of the beginning.

Application to Rheumatoid Arthritis. The reasoning leading to this discovery was clearly outlined by Hench and his co-workers.[848, 853, 855, 857] Rheumatoid arthritis was not necessarily a relentlessly progressive disease but was capable of spontaneous reversibility; remissions, partial or complete, lasting for months or years were sometimes observed, and permanent spontaneous inactivations were not rare. Certain conditions, such as febrile reactions from foreign proteins, starvation, surgical operations and anesthesia, were known to stimulate, though feebly and irregularly, the potential reversibility of the disease. More potent and more constant antagonists were pregnancy and jaundice from biliary obstruction or hepatitis. Hench, speculating that a common modus operandi might exist, was not able to harmonize the microbic theory of etiology with the powerful ameliorative influence of jaundice and pregnancy. If the agents which produced articular relief in pregnancy and jaundice were identical or similar, then the substance should be common to both sexes. Such reasoning led to the conjecture that an adrenocortical hormone might be involved, and prompted clinical trials with cortisone and corticotropin.

Initial Trials with Cortisone and Corticotropin in Rheumatoid Arthritis. In 1948 Hench, Kendall, Slocumb and Polley obtained a small supply of cortisone (then known as Kendall's Compound E) from Merck and Company, Inc. The momentous observations which followed are now medical history, and the drama surrounding the discovery is perhaps best reflected in their own descriptions of the initial case[859]:

> The first patient for whom compound E was used was a married woman 29 years old who had severe rheumatoid arthritis of four and one-half years' duration. She had not responded satisfactorily to many treatments. She was admitted . . . on July 26, 1948. Many joints were stiff, swollen, tender and painful on motion. Roentgenograms revealed destructive changes in her right hip, because of which she limped, and less extensive changes in other joints. . . .
>
> On September 20 the patient's joints were worse than they had been. On September 21 she could hardly get out of bed. On that day we began the daily intragluteal injection of 100 mg. of compound E. During that day no change was apparent; walking was so painful that she ventured only once from the room. On September 22 her improvement did not appear significant to us. But when she awoke on September 23 she rolled over in bed with ease, and noted much less muscular soreness. On September 24, painful morning stiffness was entirely gone. Scarcely able to walk three days previously, the patient now walked with only a slight limp. Her appetite was increased.

By September 27, a week after the administration of compound E was begun, articular as well as muscular stiffness had almost completely disappeared, and tenderness and pain on motion, and even swellings, were markedly lessened. The next day she shopped downtown for three hours, feeling tired thereafter, but not sore or stiff. . . .

After eight days of use of a daily dose of 100 mg. the dose was reduced to 50 mg. daily for four days, then 25 mg. daily for 10 days. But these doses were inadequate. Rheumatic symptoms increased.

The preliminary report [853] included observations on 14 patients who received cortisone and two who received corticotropin; the rheumatoid arthritis was severe or moderately severe in each instance. The administration of cortisone or of its acetate resulted in prompt and striking improvement in the musculoskeletal, constitutional and laboratory manifestations of the disease in each case. In nine patients cortisone was given for short periods ranging from eight to 61 days. In eight of these nine patients the symptoms and signs began to reappear within two to four days after the hormone was stopped; one patient retained most of the improvement for five months after cessation of the drug. Five patients received cortisone either continuously or intermittently for longer periods of two to four months. While receiving the drug they were almost, but not entirely, symptom-free; but interruptions of treatment resulted in prompt exacerbations of the disease. Prolonged administration of cortisone in one patient produced signs of hyperadrenalism, which disappeared when the hormone was discontinued. Two patients with severe rheumatoid arthritis received corticotropin intramuscularly for 12 days. Clinical improvement occurred promptly and was essentially similar to that which resulted from cortisone.

These observations were first confirmed by Bauer, Boland, Freyberg, Holbrook, and Rosenberg before the Seventh International Congress on Rheumatic Diseases; a total of nine patients with severe or moderately severe rheumatoid arthritis given cortisone for only a few days was reported—rapid and dramatic improvement occurred in each patient. Within the next few months confirmation appeared in a number of reports.[110, 177, 897, 1206, 1348, 1627, 1806, 2035, 2056]

Effects on Manifestations of Rheumatoid Arthritis. During the period covered by this review, several hundred patients with rheumatoid arthritis were reported who had received either cortisone or corticotropin for periods ranging from a few days to a number of months. In almost every instance there was rapid and impressive improvement of the reversible manifestations of the disease when adequate doses of either hormone were employed. Without exception the early reports of others [60, 176, 177, 219, 352, 597, 683, 1700, 1897, 2055, 2056, 2057] corroborated the detailed and carefully documented observations of Hench, Kendall, Slocumb and Polley.[850, 853, 854, 855, 856, 857]

Pattern of Clinical Improvement. The initial pattern of clinical improvement was quite characteristic and, provided appropriate doses were employed, the results from cortisone and corticotropin were much the same. Uniformly, there was at first a lessening of subjective phenomena, and later, with continued administration, the objective features of the disease improved.

Usually the first symptoms to diminish were muscular and articular stiffness and aching, and within one to four days, sometimes within a few hours, there was no need

for analgesics. Next in order of improvement were lessening of articular pain with motion, decreased tenderness of the joints and increased range of movement. Reductions in articular swellings were generally slower in occurring, but as a rule they were definite within the first seven to 14 days; effusions often receded rapidly but sometimes did not disappear completely even after prolonged administration. Ordinarily some joint thickening or bogginess remained, showing that the process was not completely corrected. Mild flexion deformities often disappeared within seven to 10 days, and in spite of pronounced muscle atrophy and previously restricted joint motion, muscle strength and joint function often returned to a remarkable degree within a matter of days.

Maximal initial objective improvement usually took place within the first two to four weeks, but maximal over-all improvement, with the hormones being continued, at times did not occur for two or three months. In early and less severe cases, almost complete remission could result with disappearance of all or most abnormal physical signs. In more severe cases and in cases of longer standing, some articular swelling, tenderness and pain on forced motion usually persisted even when large doses of the hormones were given for protracted periods. Fixed deformities or ankyloses resulting from cartilaginous and osseous destruction and fibrous contractures of long standing were not benefited. Nonarticular features, such as subcutaneous nodules, enlarged lymph nodes, bursitis and tenovaginitis, tended to improve or disappear along with the subsidence of joint manifestations.

Constitutional symptoms which characterize the disease usually improved rapidly; improved sense of well-being was produced and "toxic feelings" were lost or lessened; appetites quickened and there were coinciding increases in food consumption and gains in weight; general strength and endurance were enhanced; fever, if present, usually disappeared.

Abnormal laboratory findings tended to change toward normal. Anemia was improved and sedimentation rates usually decreased, often rapidly. Plasma proteins, if abnormal, reverted toward normal. [Certain serologic reactions appear to be exceptions; the streptococcus agglutination reaction and the sensitized sheep-cell agglutination reactions are usually not altered. The alterations in other laboratory findings are discussed under "The Adrenals and Rheumatic Diseases."—Ed.]

Effects on Pathologic Changes. The pathologic alteration of the disease improved but did not completely disappear. Synovial biopsies before and during hormone administration in seven patients showed reduction of synovial inflammation in each case, consisting of decrease in the number of plasma cells and lymphocytes, reduction in papillary tufting, lessening of fibrin deposits, decrease of edema and evidence of fibrous healing. The degree of histologic improvement varied with the duration of hormone administration and with the patient's individual response to them, but in no instance was the synovial membrane restored to normal.[854, 857] Similar findings were reported in one patient treated with corticotropin; measurable abnormalities (in viscosity, cell counts, character of mucin, serum-fluid glucose differences, etc.) of the synovial fluid also showed favorable response.[110] Intra-articular temperature decreased, usually within a few hours, after large initial doses of cortisone or corticotropin.[910]

Course Following Discontinuance of the Hormones. The benefits usually lasted only as long as cortisone and corticotropin were given. Their withdrawal almost always resulted in a return of the disease manifestations. Ordinarily symptoms began to return within two to five days, and then progressively increased for two to four weeks until they reached their pretreatment intensity.

In some patients the relapse was sudden and severe, especially if administration was stopped abruptly. In other patients rheumatic activity returned more slowly, over a period of several weeks or even months. In Hench's experience, about 75 per cent of cases had a quick return of symptoms, but remission was seen in about one fourth of cases, sometimes for several months.[857] In the experience of others,[175, 178, 597, 602, 1348] only an occasional patient retained much relief for a prolonged period following withdrawal of the hormone, regardless of the length of administration. Occasionally a patient suffered a short relapse and then regained much of the previous improvement. From the practical standpoint, the suppressive action of cortisone and corticotropin had to be considered as temporary, and in most cases sustained improvement from the hormones was contingent on their more or less continued administration.[178, 597, 1700]

Sudden cessation of either cortisone or corticotropin may be followed by exhaustion and muscular weakness lasting two to four weeks; and, coincidently, there may be a severe relapse of articular symptoms. This phenomenon has been attributed to temporary inhibition of adrenal cortical or anterior pituitary function provoked by the hormones. To minimize symptoms of relative adrenal insufficiency, a gradual tapering down of hormonal dosage rather than sudden withdrawal was recommended.[178, 854, 855, 2058]

Routes of Administration. During early clinical trials cortisone was administered entirely by the intramuscular route. In 1950 Freyberg and associates[603] announced that cortisone was effective when given orally and that the amounts needed were surprisingly similar to the intramuscular dosage. Their observations were promptly confirmed.[851, 1158] The antirheumatic effects of cortisone were found to appear more rapidly and to be dissipated more quickly with oral than with intramuscular administration. The effective oral dose approximated the intramuscular dose; in some patients somewhat larger amounts, ranging from one fifth to one third more, were needed by mouth. [Because it provides easier administration, less over-all expense and smoother symptomatic control, oral cortisone is now generally preferred. Results are best when the total daily requirement is divided into four doses, taken at mealtimes and at bedtime. An occasional patient responds better to intramuscular administration, presumably because alimentary absorption of the hormone is faulty.—Ed.]

Corticotropin is inactivated by gastrointestinal enzymes and is effective only when given parenterally. Standard aqueous preparations given intramuscularly are rapidly absorbed and metabolized[2056, 2057]; optimal frequency for their administration is approximately every six hours, the total requirement being divided into four equal parts. [Small amounts of aqueous corticotropin, diluted in solutions such as 5 per cent glucose in water and administered intravenously, may cause a rapid and striking clinical response, but this method has no apparent place in the continuing treatment of rheumatoid arthritis. In efforts to develop a long-acting preparation which will provide uniform continuous adrenal cortical stimulation from a single daily intramuscular injection, a number of retarding vehicles have been added to the hormone; mixtures with gelatins produced in 1952 seem fairly satisfactory for this purpose.—Ed.]

Dosage and Plan of Administration. In terms of hormonal substitution therapy, the amounts of cortisone and corticotropin required to suppress the manifestations of rheumatoid arthritis are large; effective doses of cortisone, for example, may be several times as great as those needed to sustain patients with Addison's disease.

Hench, Kendall, Slocumb and Polley[853, 854, 857] gave cortisone intramuscularly in doses of approximately 100 mg. a day to their first patients, and later used

300 mg. on the first day and 100 mg. daily thereafter. Dosages of corticotropin varied but in general the effective daily dose was, milligram for milligram, approximately one-half that of cortisone.[854] Smaller amounts of cortisone were tried in some cases (all with severe disease), but amounts of 25 to 75 mg. a day were either inadequate or ineffective. Later experience indicated that although the high doses employed during early investigations allowed the antirheumatic properties of the hormones to be established unequivocally, such doses might not always be necessary.[857]

Boland and Headley[177] observed that smaller doses of cortisone (such as 50 mg. a day) were adequate for patients whose disease was only mildly or moderately active, and later they demonstrated that some cases of more severe rheumatoid arthritis could be satisfactorily controlled with moderate dosage (50 to 75 mg. a day), provided the arthritis was first brought under control with larger amounts of hormone.[178] Good results were maintained in some patients from injections of 100 to 150 mg. of cortisone every other day or even three times a week.[175, 176, 597] Similar success with corticotropin in smaller doses (total of 10 to 30 mg. a day) was obtained.[907, 1296, 1627]

From attempts to establish cortisone and corticotropin as practical treatment agents it was obvious that schemes of administration had to be devised which would avoid or minimize hormonal complications and yet preserve clinical improvement. It became evident that dosages had to be individualized and guided by considerations of both safety and clinical response. These in turn appeared to be influenced by many factors, including individual differences in susceptibility to the drugs, severity or activity of the disease, age and sex of the patient, presence or absence of relative contraindications, the plan of administration, coöperation of the patient, the care and skill used by the physician in patient management, and by other contingencies. Various schemes for administering cortisone and corticotropin were investigated, each having advantages and disadvantages.[175, 178, 597, 854, 857, 1700] Two main plans evolved: (1) intermittent administration of one or the other hormone, given in courses lasting a few weeks at a time, the courses being separated by treatment-free intervals; and (2) more or less continuous administration for a prolonged, indefinite time, employing the smallest doses compatible with the maintenance of good (not necessarily complete) relief and the avoidance of significant hormonal side effects or relapse.

Hench and co-workers suggested at first that the interrupted or "course" method might provide a more physiologic type of response, lessen the incidence of side effects, and theoretically permit physiologic and histologic recovery of the pituitary and adrenal glands during the rest periods. Remissions lasting weeks or months were seen in approximately 10 per cent of patients so treated, and some patients seemed to relapse less severely with successive courses. However, relapses developed between courses in most instances, and patients usually were unwilling to accept a return of symptoms even with the knowledge that relief would again ensue with the next course; from the standpoint of patient rehabilitation, alternating periods of relief and relapse were not satisfactory.

Uninterrupted treatment plans were studied by Boland and Headley,[175, 178] Freyberg[602] and others.[857, 1296, 1700] Dosage schemes were prompted by three preliminary observations: (1) the amounts of hormone needed for effective control depended more on the severity or activity of the rheumatoid arthritis than

on other factors; (2) adequate symptomatic control could be supported by smaller, better tolerated doses in many cases, provided the rheumatic manifestations were first suppressed by larger amounts of hormone; (3) the incidence and severity of hormonal complications were decidedly less when smaller doses were used. Programs such as the following were recommended [178]:

Initial Suppressive Doses: For severe and moderately severe cases 200 or 300 mg. of cortisone are given for one or two days, followed thereafter by 100 mg. daily. For moderate and mild cases 100 mg. are given on the first and subsequent days. These suppressive amounts are continued until the clinical manifestations are brought under control. The period required for this may range from seven to 36 days; in general, the time lengthens with the severity of the disease.

Reduction in Dosage: When rheumatic activity is satisfactorily suppressed with larger doses, the daily amounts of hormone are gradually decreased in a steplike manner. Gradual reductions are necessary because the disease may escape control if the dose is abruptly lowered, and stepdowns in dosage are made more slowly in severe than in less severe cases. Reductions are usually accomplished at intervals of every four to seven days or longer—by decrements of 10 mg. with cortisone given intramuscularly, and of 12.5 mg. with oral medication.

Maintenance Doses: The smallest daily amount which will adequately control the clinical manifestations is considered as the maintenance dose. Attempts are not made to restrain the disease completely, unless this can be accomplished with relatively small doses. Once established, the maintenance dose is continued without interruption. In most cases the amount is not fixed, however, as adjustments in dosage are required from time to time to meet fluctuations in disease activity.

[With increasing experience since 1950, there has been a definite trend toward use of smaller doses, particularly in initiating treatment. With oral cortisone, doses larger than 100 mg. a day are rarely indicated during the first few days of treatment and may be undesirable. Stepwise reduction of dosage has tended to be more gradual. There is difference of opinion as to what may be considered a "safe" maintenance dose for indefinite administration. All members of the Editorial Board agree that it should not exceed 75 mg. a day; most of us would place an upper limit of 50 mg. daily on maintenance doses for women. A few of us feel that, with few exceptions, such maintenance dose should not exceed 37.5 mg. of cortisone daily for women, and 62.5 mg. daily for men. There appears to be greater individual variation in responsiveness to corticotropin, and range of dosage with this agent has not been well defined.—Ed.]

The disadvantages of the continuous therapy plan are (1) an increased liability to untoward side effects if relatively high maintenance doses are required; (2) hazards, as yet poorly defined, related to prolonged interference with the pituitary-adrenal system, such as possible masking of intercurrent infections, uncertain effects from prolonged adrenal cortical atrophy (from cortisone), or hypertrophy (from corticotropin); (3) the possibility of developing temporary refractoriness to the drugs. However, the hope for prolonged relief has given the plan strong appeal to physicians and patients, and the introduction of oral cortisone has facilitated its use.

Results. Hench and colleagues [854, 857] reported relatively short-term results in 27 patients, all of whom had either severe or moderately severe rheumatoid arthritis. Among the 21 patients who received cortisone (usually 100 mg. daily) the antirheumatic response was graded as very marked in 12 (57 per cent), marked in eight (38 per cent), and moderate in one (5 per cent). With the large doses used, the over-all relief was roughly 80 to 90 per cent. A total of 35 "courses" of cortisone was given to the 21 patients, the courses varying from

eight to 187 days in duration, but most of them ranging from 14 to 60 days; the response to individual courses was graded as very marked in 15, marked in 18, moderate in one and mild in one. If 300 mg. of the hormone were given the first day, the onset of improvement was usually prompt (three to 14 hours), but when initial doses of 100 mg. were administered it was somewhat more tardy; a 300 mg. dose on the first day did not, however, hasten significantly the maximal response. In those patients who received more than one course of cortisone, the pattern of improvement was essentially the same with each course. Corticotropin (45 to 140 mg. per day) was administered to six patients for periods of from 11 to 87 days; very marked improvement (75 to 90 per cent) was seen in two. Initial response became maximal within seven to 12 days, and with continued administration further gradual improvement occurred.

With the use of these relatively large doses of cortisone or corticotropin, hormonal effects were noted in 61 per cent of cases; they were graded as mild in 35 per cent, moderate in 9 per cent, and marked or "more disturbing" in 17 per cent. Most patients tolerated well 100 mg. of cortisone or a corresponding amount of corticotropin daily for at least a month or two. [Endocrine complications are discussed in the section on "The Adrenals and Rheumatic Diseases."—Ed.]

Favorable responses to short-term cortisone or corticotropin administration were recorded by others.[60, 177, 219, 252, 597, 683, 907, 1221, 1296, 1348, 1494, 1896, 1969, 2056, 2057] McEwen and Bunim[1348] reported immediate results in 18 patients with rheumatoid arthritis who received cortisone: 13 experienced very marked improvement, one was markedly improved, three showed moderate improvement, two only slight improvement, and one failed to respond. Essentially similar results were noted in 11 patients who were given corticotropin. In the majority of cases, relapse began within two to 14 days following cessation of therapy with either hormone.

Using a plan designed for long-term therapy (initial large suppressive doses, gradual dose reduction, and then uninterrupted administration of smaller doses), Boland and Headley[175, 178] reported results in 42 patients with rheumatoid arthritis treated with cortisone intramuscularly for two to six months. Response to initial suppressive doses was considered very marked in 20 (47.5 per cent), marked in 13 (31 per cent), and moderate in eight (19 per cent), with no improvement in one (2.5 per cent). Thirty-three of the 42 patients (78.5 per cent) experienced more than 75 per cent relief of their over-all disability. The results from initial large doses were distinctly better in less severe cases; improvement was very marked or marked in 50 per cent of severe cases, 93 per cent of moderately severe cases, 88 per cent of moderate cases, and 100 per cent of mild cases. Once the disease was suppressed by initial large doses and the doses then gradually reduced, satisfactory improvement was maintained with doses ranging from 32 to 65 mg. per day in 32 patients (76 per cent). Best results were obtained in patients with less severe rheumatoid arthritis; with doses averaging 65 mg. a day or less, satisfactory antirheumatic control was maintained for periods up to six months in 35 per cent of severe cases, and in over 90 per cent of less severe cases. Maintenance dosages, once established, were fairly constant but not fixed, and they were manipulated by small increments or decrements from time to time to meet fluctuations in disease activity; for major flare-ups of rheumatic symptoms, "booster doses" of 100 mg. a day for four or five days were sometimes employed. When the maintenance dose was 65 mg. a day or less, significant adverse effects

appeared in 8.3 per cent of cases, while they developed in 33 per cent of patients maintained on 100 mg. a day. They concluded that some severe cases and most moderately severe, moderate and mild cases of rheumatoid arthritis may be kept under adequate clinical control and with relative safety, at least for periods of up to six months, with smaller maintenance doses of cortisone, provided larger doses to suppress the disease are employed initially. [Subsequent experience with maintenance dosage for periods of as long as two years or more has indicated that the percentage of patients who can be satisfactorily controlled decreases as the duration of treatment increases. Often satisfactory control is lost during the ninth to eighteenth month of treatment. Osteoporosis, masking of intercurrent infections, and possibly activation of peptic ulcer, or of healed tuberculosis, are potential complications of long-term therapy.—Ed.]

Limitations and Dangers. In their early papers, Hench, Kendall, Slocumb and Polley cautiously considered their observations as investigations in clinical physiology rather than therapy.[853, 854, 857] Widened experience and trials with various dosage plans, particularly smaller maintenance schedules, soon indicated that cortisone and corticotropin could be applied practically, though restrictedly, as treatment agents for rheumatoid arthritis. Actual therapeutic use of the hormones has been beset with problems. Most of these have stemmed from the following considerations: (1) The benefits derived from the hormones are temporary and suppressive only, not curative. (2) They must be administered more or less continuously for an indefinite period of time if improvement is to be sustained. (3) The hormones, in addition to their antirheumatic action, produce manifold physiologic responses in various organs and tissues, and these may become clinically manifest as adverse hormonal complications, especially when large doses are employed for long periods. (4) Certain coexisting pathologic conditions may be aggravated by the hormones and serve as relative or absolute contraindications for their use. (5) Refractoriness to the drugs eventually develops in some cases after long periods of administration; in other cases the disease, though suppressed symptomatically, seems to progress during treatment. (6) Long continued use of the hormones results in histologic and functional changes, though reversible, in the adrenal cortices and anterior pituitary gland. (7) Optimal methods of administration and patient management have not yet been established. Although the problems were recognized they were not fully explored during the period covered by this review.

[Some opinions and conclusions from more extensive studies reported since 1950 may be summarized as follows:

1. Cortisone or corticotropin should not be recommended for all cases of rheumatoid arthritis. Adequate trials should first be made with more conservative and simpler methods; if these fail to provide satisfactory symptomatic control, then the use of cortisone may be considered. Improvement may be expected in only those manifestations due to active disease, not those resulting from irreversible structural damage.

2. Absolute contraindications should be ruled out before beginning treatment; currently, these include active infection such as tuberculosis, syphilis or poliomyelitis, psychoses or severe psychoneuroses, active peptic ulcer, marked renal insufficiency from any cause, and Cushing's syndrome. Relative contraindications should be weighed carefully; the risk of administering cortisone is increased by the presence of certain conditions, i.e., arrested tuberculosis, cardiovascular or renal disease, diabetes mellitus of any degree, tendency to thromboembolic phenomena, osteoporosis and convulsive disorders. The status of pregnancy is uncertain, but therapy generally is not needed during the latter months of gestation.

3. Satisfactory rheumatic control should not be expected in all patients with rheumatoid

arthritis. Experience with large series of patients has apparently varied considerably. Some of us estimate the proportion of patients who can be safely maintained in worthwhile remission for one and one-half to two years to be not over 25 per cent; others feel that adequate improvement can be maintained for long periods in approximately one-half of patients. These differences undoubtedly reflect differences in severity of the disease and in judgment as to the degree of hyperadrenal manifestations which can be safely tolerated. Most frequent failures are among patients with severe or very active disease whose dosage requirements for good rheumatic control turn out to be larger than can be tolerated.

4. Because continued large doses almost invariably lead to endocrine complications, it is wise to be content with the best results which can be maintained from "safe" levels of dosage. If adequate relief cannot be provided by such dosage, then the patient and physician should settle for less than satisfactory control, or discontinue hormonal therapy.

5. The hormones should not be relied on exclusively for treatment. Other measures, such as adequate rest, avoidance of trauma, physiotherapy, and salicylates (and, according to some, chrysotherapy), should be used concurrently.

6. Should relative refractoriness eventually develop and improvement deteriorate despite increasing and eventually prohibitive amounts of hormone, responsiveness usually returns if the drug is withdrawn for two or three months.

7. All the potential risks implicit in therapeutic use of cortisone and corticotropin have not been determined, but certain general observations regarding endocrine complications seem to be agreed upon: (*a*) most are fully reversible and disappear fairly promptly with reduction of dosage or cessation of administration; (*b*) although individuals differ in susceptibility, the incidence and severity of unwanted reactions vary directly with the size of the dose employed; (*c*) when the hormones are given cautiously in reasonable doses and in the absence of contraindications, complications, if they occur, are usually minor or transient and of little consequence; (*d*) most minor complications are signals for caution, perhaps for dosage reduction, but are not indications for discontinuance of therapy; (*e*) serious reactions are uncommon unless the hormones are given in excessive amounts for long periods or in the presence of contraindications; (*f*) their incidence does not increase appreciably with prolongation of therapy, provided the maintenance doses used are small; (*g*) they are more prone to develop in women than in men; (*h*) their incidence is particularly high in children because the doses required may be almost as large as for adults, and for body size much greater; (*i*) judicious manipulation of dosage is the most efficient means of managing or preventing hormonal complications, but in many instances good therapeutic control may be lost when the dosage is reduced. Certain complications may be regulated by simple procedures alone (salt restriction or diuretics for edema, low-calorie diet for weight gain, etc.); failure to invoke such measures sometimes causes physicians to abandon effective doses prematurely. Some authorities recommend a salt-poor diet when maintenance doses of more than 50 mg. a day are used, and prescribe low-calorie regimens as soon as the patient approaches optimal body weight.

8. Serious problems may be encountered in withdrawing these hormones from patients who have been on maintenance treatment for several months. Some of these are concerned with suppression of endogenous pituitary-adrenal function and can be minimized by gradual withdrawal. Others are related to a flare-up of the rheumatoid process which occasionally defies all efforts in management.

9. To some workers, the experience of indefinite administration with a progressively diminishing proportion of satisfactory results has been discouraging, and has led them to restrict the use of cortisone and corticotropin to patients (*a*) in whom they can be used for a predictable period of time to facilitate other measures in a rehabilitation program; (*b*) who show a progressive downhill course resistant to other measures of treatment, or (*c*) in whom small doses have been found to give worthwhile improvement in function.—Ed.]

Attempts to Potentiate Action of Cortisone and Corticotropin. Despite attempts to find an adjunctive agent which would fortify or prolong the action of cortisone or corticotropin, no combination with other substances has been proved by critical studies to have value greater than use of the hormones alone.[1700] Working on the hypothesis that insulin may function as a synergist to cortisone, the two hormones were given conjointly to 12 patients with rheumatoid arthritis. With small doses of

cortisone acetate (12.5 mg. intramuscularly) and 20 units of insulin given daily for 10 days, no clinical improvement was noted. But when the dosages were advanced to 50 mg. of cortisone and 40 units of insulin a day for 10 days, marked improvement was noted; in 10 patients the erythrocyte sedimentation rates returned to normal and in eight patients "clinical reversals, Grades I and II" (Steinbrocker's classification), were claimed.[861] Sodium para-aminobenzoate was reported to act synergistically with cortisone. In three patients, relapse developed when the dosage of cortisone was reduced from 100 mg. to 25 mg. intramuscularly a day, but with the addition of sodium para-aminobenzoate (in total doses of 12.0 gm. a day by mouth), previous improvement was recovered. With this combination, it was claimed that satisfactory degrees of improvement were retained by doses of cortisone which otherwise were too small to be effective.[2165] [Other observers have failed to substantiate this claim.—Ed.] Attempts to modify the antirheumatic action of cortisone by giving desoxycorticosterone [1551] or adenosinetriphosphate [597] were unsuccessful.

Search for Substitutes. Intensive efforts were made to find an effective yet less hazardous, more abundant or less costly substitute for cortisone or corticotropin. Many steroids, some closely related structurally to cortisone, and other substances have been therapeutically screened. Published results of these clinical tests have been extraordinarily conflicting, and often so contradictory that the reader, after reviewing them, is left in a state of bewilderment. In general, the early enthusiastic claims made for one compound or another have been mostly or completely discredited by later and more critical studies. Analysis of the extensive data which have accumulated leads to the conclusion that, apart from hydrocortisone (Kendall's Compound F), no substance has been found to possess antiinflammatory properties comparable to those of cortisone or corticotropin. On the basis of various clinical and biologic studies to date, it appears that the antirheumatic activity of steroid compounds is dependent on a precise chemical configuration.[1587]

Other Steroids. Lewin and Wassen [1209] reported striking immediate amelioration of rheumatoid arthritis after the intramuscular administration of 5 mg. of desoxycorticosterone acetate followed by an intravenous or intramuscular injection of 1,000 mg. of ascorbic acid. The effects usually lasted two to six hours, occasionally more than 24 hours, and were said to endure longer with each successive injection. Their observations were soon corroborated by LeVay and Loxton,[1198] and in full or in part by others.[125, 756, 1199] Subsequent investigators, however, have been unable to confirm these results. The overwhelming opinion is that desoxycorticosterone, with or without ascorbic acid,[264, 278, 450, 602, 694, 979, 1074, 1119, 1897, 1969, 2152] or with riboflavin,[1073] has little or no influence on the activity or progression of rheumatoid arthritis and that it is useless as a therapeutic agent.

Because there is evidence of great increase in progesterone production during pregnancy, progesterone was administered intramuscularly in daily doses of 50 mg. to 21 patients for 30 days; clinical improvement of varying degrees was observed in 15 cases.[1655] But carefully conducted investigations by others [21, 352, 368, 597, 602, 1073, 1159, 2046] have failed to substantiate claims for progesterone or anhydrohydroxyprogesterone. Delta-5-pregnenolone, used either intramuscularly or orally, was reported by several authors [405, 588, 1977] as favorably altering the clinical picture of peripheral rheumatoid arthritis and ankylosing spondylitis, although results were admittedly less rapidly apparent than when cortisone was employed. However, when the substance was assessed by others,[352, 368, 509, 556, 784, 1969] no evidence of cortisone-like activity or significant antirheumatic influence was noted, or the response was equivocal.[1966] Seifter,

Warter and Fitch [1801] believed that 21-acetoxypregnenolone caused, within two to eight days, significant reduction of articular pain and swelling, together with increased joint motion; but others found the compound devoid of antirheumatic activity.[368, 597, 1587]

Ishmael and co-workers [962] claimed that, of 90 patients with rheumatoid arthritis treated with 100 to 300 mg. daily of testosterone propionate intramuscularly, approximately 65 per cent showed decided improvement within 24 hours. Testosterone combined with progesterone alone or with pregnenolone in various ways was said to have induced remissions in 81 of 90 patients; details of dosage and methods of manipulating and combining the steroids were vaguely stated. The claims for testosterone, with or without other steroids, have not been verified by critical studies.[219, 352, 368, 597, 602, 734] Other steroid compounds have failed to yield significant results, at least in the range of dosage so far explored; these include, among others, 11-desoxycortisone (Reichstein's Substance S) [597, 2046] and 11-dehydrocorticosterone (Kendall's Compound A).[734, 853] Trials with massive doses of human chorionic gonadotropin (Pregnyl) were not rewarding.[47, 1074]

Attempts to Stimulate Release of ACTH. Epinephrine, 0.5 mg. given subcutaneously every six hours to two patients, resulted in "very slight but definite improvement" in their rheumatoid arthritis, but with continued administration the drug lost its effectiveness as an adrenocortical stimulator.[2055, 2057] One patient with advanced rheumatoid arthritis was reported to benefit from such treatment,[656] but no improvement was noted in 11 of 12 patients subjected to the procedure by others.[734] [Extensive studies indicate that epinephrine cannot be relied on to stimulate the pituitary adrenal mechanism.—Ed.] In view of evidence that insulin hypoglycemia liberates epinephrine, and of conjectures that electroshock therapy may stimulate pituitary-adrenal function, possible benefits from these reactions were explored by Kersley and co-workers.[1076] Hypoglycemic reactions from insulin were induced every morning for five days each week over a period of three to four weeks in 40 patients with active rheumatoid arthritis; improvement was considered marked in 22 and slight in nine, and nine showed no improvement; in 10 patients the benefits continued for six weeks after completion of treatment. Electroshock therapy was given to 11 patients (average of five shocks each): three showed marked temporary improvement, three slight improvement, and five no change. [Laboratory studies did not clearly support the concept that these agents acted through the pituitary-adrenal mechanism. Further carefully controlled studies with insulin would appear worth while. The authors warned: "insulin hypoglycemia should not be looked upon as a new treatment for rheumatoid arthritis."—Ed.]

Other Aspects of Treatment

Analgesics. For relief of pain, no drug stands up so well as acetylsalicylic acid.[297] In ordinary therapeutic doses it apparently does no harm even though it is taken indefinitely [317]; gastric irritation may be controlled by prescribing enteric-coated tablets,[311, 2024] and there seems to be no justification for employing salicylates intravenously.

In attempts to enhance or prolong their action, salicylates have been tried in combination with other substances. A mixture of sodium salicylate and sodium para-aminobenzoate was reported to produce superior and longer pain relief than sodium salicylate alone.[1870] Most workers have failed to confirm the enthusiastic and widely publicized claims made in 1947 for a mixture of acetylsalicylic acid and calcium succinate [2018]; the product appeared to have no value over aspirin alone.[368] Sodium gentisate was said to exert antirheumatic effects equal to, or greater than, those of salicylates,[1878] and tetraethylammonium bromide given intramuscularly was reported as an efficient analgesic during exacerbations of the disease.[939] Because of the danger

of habit formation, opiates and Demerol were again condemned. Dimethylaminoheptanone-methadon (Dolophine), in oral doses of 2.5 mg., was effective in controlling pain in nine of 14 patients with rheumatoid arthritis,[963] but the drug is classified as a narcotic, and unpleasant side effects, including nausea, are not uncommon.

Variable degrees of pain relief were claimed in about 50 per cent of cases of rheumatoid arthritis by infusing a solution of procaine intravenously.[704, 707] Objective evidence of improvement from repeated injections rarely occurred, and the relief usually lasted little longer than the duration of the infusion [1304]; the results obtained in most instances were not worth the expense of hospitalization.[1645]

Rest and Motion. The value of rest, both mental and physical, was universally recognized,[317, 421, 1067, 1078, 1557, 1777, 2036] often as the keynote to successful therapy.[297, 300] But rest should not mean the total immobilization or "mummification" of the patient.[64] Complete bed-rest is rarely indicated except during acute febrile stages, during severe exacerbation of joint manifestations, or during the initial phases of treatment. Over-resting encourages muscle atrophy, contractures and ankylosis [1549]; some patients, overconscientious about rest and fearful of pain, may learn that "the price of too much comfort is crippledom." [1382] Pain signals the patient that he has overexercised, but the effects of over-rest are insidious. Between the rest which a sore, inflamed joint should have and the activity needed for psychiatric and financial reasons, the doctor must choose a just course [1820]: the patient should be warned against excessive weight-bearing and repeated aimless movements of involved joints; he should not "hurry and worry" but should take enough nonfatiguing exercise to improve posture and to maintain mobilization and alignment of joints. The amount of bed-rest should be modified from a basic minimum of 10 hours in bed each night and one hour of rest each morning and afternoon.[1565, 1820]

When prolonged bed-rest is needed, adequate posture should be maintained and bed exercises instituted.[1231, 1621, 1642] The bed should be firm and nonsagging, pillows under the knees or shoulders should not be used, and indicated supports with sand bags or foot board must be provided. Bed calisthenics, with breathing, muscle-setting and trunk-stretching exercises, should be carried out several times daily, these being carefully timed to alternate with periods of rest.[811] All joints, even though acutely inflamed, should be carried gently through the maximal range of motion once or more daily.[1549] The analgesia from salicylates given beforehand increases the patient's ability to exercise.

Diet. There is no specific diet. Because most patients with rheumatoid arthritis are undernourished and underweight, effort must be made to maintain nutrition at its highest point by a well balanced diet,[311, 317, 1067, 1408, 2000] high in calories and vitamins, rich in fruits and vegetables, and with a normal ratio between protein, carbohydrate and fat.[2060] When regular diets are found deficient in protein, dietary supplements, such as protein hydrolysate with vitamin B factors (and sometimes with a "chaser of Karo syrup"), may be valuable in promoting weight gain.[2123]

Vitamins. As the absorption of dietary vitamins is faulty in debilitated individuals, supplementary vitamin therapy would seem indicated,[1794, 1820] but there is no specific vitamin for rheumatoid arthritis and, at best, vitamins play only a supportive rôle.[1645, 2065] Neither the symptoms nor the course of rheumatoid arthritis was altered directly by the administration of vitamin A, vitamin B complex (thiamine hydrochloride, niacin, riboflavin), vitamin C, E or K.[2065]

Peripheral nerve involvement sometimes occurred as a part of the disease, but pains of neuritic origin were seldom alleviated by the administration of thiamine hydrochloride. Niacin administered orally or parenterally caused a transient flushing phenomenon and seemed to produce temporary relief similar to the effects of a hot bath, but had no effect on the disease process.[2065] Requirements for vitamin C in patients with rheumatoid arthritis may be increased, for the majority of patients have low plasma ascorbic acid levels. Supplements of ascorbic acid or natural fruit juices in quantities sufficient to maintain normal plasma values failed to alter the course of the disease.[2065] Capillary fragility was frequently increased in patients with rheumatoid arthritis; the abnormality was not corrected by vitamin C alone, but was improved by the use of vitamin P (hesperidin), and especially by combinations of both.[2125] Experiences with vitamin E have been disappointing in all forms of rheumatic disease [2065]; cystic mastitis may attend its use.[1645]

Vitamin D. Although a few physicians still sponsored concentrated vitamin D therapy,[329, 527, 1280] the majority of experienced rheumatologists regarded it as useless and dangerous.[317, 761, 844, 927, 1541, 2065] Rawls,[1645] after 10 years' experience, expressed the view that vitamin D "is of little or no value regardless of the preparation used." Most reports were concerned with toxic effects, manifested clinically by polydipsia, polyuria, muscle weakness and headache, and, less frequently, by drowsiness, nausea, vomiting and diarrhea.[1541, 1780]

Such symptoms were almost invariably accompanied by hypercalcemia, and at times by metastatic calcifications, especially in the kidney. Serious renal impairment may attend the intoxication [590, 831, 955, 1308, 1448, 1541, 1652] and may prove fatal.[145, 1042] Postmortem findings were characterized by calcification in different organs, mostly in the collecting tubules of the kidneys, the media of arteries, the acid-secreting cells of the stomach, the small vessels of the bronchi, bronchioles and alveoli, and the myocardium.[104] Calcifications in soft tissues, especially in the regions of the joints (in articular bursae and adjacent soft tissue),[145, 1042, 1541] in the subcutaneous tissues [956] and sclera [613] may also occur.

Correction of Anemia. The anemia associated with rheumatoid arthritis frequently fails to respond to iron salts given by mouth, at least in doses ordinarily effective in idiopathic hypochromic anemia. Intravenous injections of iron salts in large doses were recommended for resistant cases [1259, 1734, 1855]; of 51 cases so treated by Sinclair and Duthie,[1854] satisfactory rises in hemoglobin levels occurred in 38, but 13 cases remained refractory. The blood picture improved in 20 patients with rheumatoid arthritis treated with folic acid for periods of three months. Usual dosage was 20 mg. daily; but larger amounts, up to 100 mg. daily, were given if initial response was not satisfactory. Improvement consisted of an increase in mean corpuscular volume, hematocrit, hemoglobin and color index, but there was not a comparable rise in total erythrocyte or leukocyte counts.[1953] Blood transfusion was again described as a useful supportive measure [1849, 1850]; one or more transfusions will correct anemia (at least temporarily), may better the general condition, and may help in starting patients on the road to improvement.[297, 2000]

Transfusions from Pregnant or Postpartum Donors. When "several" transfusions of 300 c.c. of citrated blood from pregnant women were given to 28 patients with rheumatoid arthritis, 64 per cent were reported to have recovered or improved. Six patients, refractory to other forms of therapy, were said to have demonstrated remarkable response.[97] These results were not supported by the observations of others, and it appeared that transfusions of blood from pregnant women did not yield results superior to those following transfusions of blood from nonpregnant persons.[1586] Intravenous infusions of pooled postpartum plasma (250 c.c. each week for three to six months) were given to eight patients with active and moderately advanced rheumatoid arthritis; six similar patients were given weekly infusions of normal plasma. In the

postpartum plasma group striking clinical improvement was reported between the fourth and eighth weeks; the patients felt stronger, appetites increased, joint stiffness, pain and swelling diminished, and in two instances subcutaneous nodules disappeared. Improvement was noted in each patient, and in six patients who had been refractory or intolerant to gold salts the response was said to be dramatic. Five of the six patients given normal plasma either failed to respond or were worse; one felt better subjectively.[698, 701] [Confirmation of these results is lacking. One of us, L. M. L., has seen no improvement in eight patients after 10 to 12 weekly infusions of postpartum plasma collected and administered in the same manner as in the reported studies. The danger of transmitting homologous serum jaundice must always be considered in the use of blood and blood products.—Ed.]

Psychotherapy. "A doctor who leaves psychotherapy out of his kit will not progress very far in the treatment of rheumatoid arthritis."[300] Most patients suffer from some degree of mental depression or anxiety, and the course of the disease often fluctuates with the mental state[297, 317, 2150]; hence patients must be continually encouraged, reassured or "buoyed up," lest they develop a wheelchair or crutch philosophy.[179, 1255, 1820] But prolonged series of seances or complex psychoanalytic discussions are not required,[1642] and the managing physician can usually accomplish more than a psychiatric specialist.[601] The importance of environmental adjustment[1645] and financial aid through public assistance[64] was stressed. Swaim[2000] noted "amazing improvement" in patients when home relationships were straightened out, particularly when resentment and fear had been removed.

Management of Foci. The theory that rheumatoid arthritis is caused by infection seeded into the circulation from a distant focus has been generally abandoned,[1099, 1725] and a conservative attitude toward eradication of foci has become universal. Only definite foci should be removed, and then only as a general health measure which would be equally advisable in a patient not suffering from rheumatoid arthritis.[317, 600, 601, 1170, 1871, 1645] Some[350, 1067] believe that the "secondary type" of rheumatoid arthritis which comes on after an obvious infection may show dramatic response to removal of the specific focus, whereas eradication of foci in "idiopathic" rheumatoid arthritis is seldom helpful.

Vaccines. Most rheumatologists agreed that vaccines have no real value, whether they be autogenous or stock, or whether they be administered intravenously, subcutaneously or intradermally.[172, 600, 601] Some regarded their use as a form of psychotherapy or as a means of bringing the patient back to the office and keeping him under control while therapeutic methods which appear less spectacular may be carried out.[1082] While most have abandoned them, a few proponents of vaccines[1567, 1820] believed that recovery is aided by vaccine therapy in an appreciable number of cases. Others recommended the use of autogenous vaccines in patients with "nonspecific infective" or "secondary" types of rheumatoid (focal) arthritis.[1067, 1072] A combined antigen was said to be effective in arresting and controlling rheumatoid arthritis in 71.1 per cent of 90 patients observed for from two to four years.[2124]

Fever Therapy. Cecil[297] observed that febrile reactions induced by intravenous injections of triple typhoid vaccine would sometimes bring about rapid and complete cessation of symptoms during the initial stages of rheumatoid arthritis, especially in subacute febrile cases, but its use in chronic, well established cases was not recommended. Originally foreign protein therapy was thought to act by mobilizing the patient's antibodies, but evidence that it acted at least partly by stimulating the adrenal cortices was obtained.[30, 49] Blood flow was determined with the plethysmograph before and after artificial induction of fever in patients with rheumatoid arthritis. Fever

to 101° F. or more, whether induced actively by the intravenous administration of typhoid vaccine or passively by Kettering hypertherm and hot tub baths, produced an increase of the peripheral circulation. Intravenous administration of typhoid vaccine led to a reduction of peripheral blood flow during the chill phase.[2103] [Clinical results were not given.—Ed.]

The potential dangers from artificial hyperpyrexia were emphasized, and a fatality from intravenous injection of typhoid vaccine was reported.[123] Minor electrocardiographic changes occurred during the chill phase, reverting to normal during the flush period or during defervescence.[587] The common pathologic findings in 17 patients with fatal febrile reactions (13 induced by Kettering hypertherm cabinet, three by intravenous typhoid vaccine, and one by hot baths) were congestion of all viscera and the brain, together with purpuric hemorrhages, especially in the heart and gastrointestinal tract. These did not differ with the method of heat induction.[680]

Roentgen Therapy. Roentgen therapy for peripheral rheumatoid arthritis has been disappointing to some,[174, 599, 1621, 1645, 1725] but frequently successful in relieving local symptoms of pain and soreness in the experience of others,[1582] especially when applied to one or two large joints that remained swollen and boggy. Kuhns and Morrison [1142] treated 154 patients who had peripheral rheumatoid arthritis (without spondylitis). Improvement of the joints treated was marked in 22.7 per cent, moderate in 39.9 per cent, and slight in 16.8 per cent; no change was noted in the remaining 20.8 per cent. Benefits consisted of diminution of pain and swelling, local analgesia, and decrease in muscle spasm followed by increased range of active, painless motion. To determine the effect of suggestion, 10 patients with bilateral knee involvement were treated; one knee received roentgen therapy, but the other, although placed under the machine, received no irradiation. Definite objective improvement was observed in seven of the treated knees and in none of the untreated knees; one patient reported subjective relief in both knees. Results were best when two courses of therapy (each consisting of a total dose of 1,200 roentgen units given in divided doses of 200 "r") were applied. Radon ointment applied locally to painful joints from various causes was claimed to produce amelioration in most cases, including three cases of rheumatoid arthritis.[1980]

Chrysotherapy. The literature now contains reports of more than 7,000 cases of rheumatoid arthritis treated with gold preparations. This total experience should have provided an impressive pool of information from which precise conclusions regarding the efficacy of chrysotherapy could be drawn. But certain common denominators essential for dependable comparisons and correlations of results have been lacking,[1938] and despite such extensive experience the exact value of gold compounds has not been determined. Opinions remain diverse. Many critical rheumatologists maintain their convictions that chrysotherapy is the best single remedy available for rheumatoid arthritis.[297, 844] These were not sensational statements, considering how disappointing most other remedies are (Cecil).

Indications. With the exception of palindromic rheumatism, rheumatoid arthritis appears to be the only rheumatic disease in which the use of gold compounds is indicated.[286, 598, 1831] Not all cases should receive chrysotherapy; the physician should be convinced that the disease is active and progressive, and a reasonable trial of conservative measures should be given first. Some contended that gold salt therapy should be "a last resort," withheld until all other measures had failed. Others urged that it be instituted as early as possible, preferably within the first two years of the disease, before irreversible changes have taken place.[1071, 1072] "It is a pernicious doctrine to advocate the use of gold only after everything else has been tried" (Cecil). Some

were convinced that the early use of gold will prevent many of the sequelae now observed in patients with long-standing arthritis. The patient should always understand the risk involved, but the facts should not be distorted or the dangers oversold, and the responsibilities must be assumed coöperatively by the patient and the physician.[845, 2225]

Contraindications. Again listed were the generally accepted contraindications: severe diabetes mellitus, disseminated lupus erythematosus, nephritis, ulcerative colitis, hepatic damage, blood dyscrasias and hemorrhagic tendencies, pregnancy, and history of previous exfoliative dermatitis.[172, 328, 1071, 1149, 1470] Vascular hypertension and chronic valvular heart disease were not considered contraindications,[295] nor was pregnancy,[598] although the arthritis usually improves so much during pregnancy that gold therapy is seldom needed.

Preparations. Of the gold compounds popularly used in America, soluble compounds include gold thioglucose (Solganal-B Oleosum), gold sodium thiomalate (Myochrysine), and gold sodium thiosulfate (Sanocrysin); insoluble compounds include gold calcium thiomalate and gold thioglycolanilide (Lauron). The gold content is believed to determine therapeutic activity.[1831] The water-soluble compounds are more rapidly absorbed and appear to have therapeutic advantages [1831]; gold calcium thiomalate was considered by Kersley [1069] to be slightly less toxic than the soluble gold sodium thiomalate; gold thioglycolanilide was claimed to be just as efficacious as soluble preparations and less toxic,[1690] but others found it therapeutically undependable [598] and questioned its alleged lower toxicity.[1624] Colloidal gold preparations, such as gold sulfide (Aurol-Sulfide) and colloidal metallic gold [1819] are rapidly phagocytosed in reticuloendothelial cells, especially in the liver and spleen; hence, although toxicity is prevented, therapeutic activity is minimal.[334, 1831]

Mode of Action. The mode of action of gold compounds remains unknown.[598] Studies of their pharmacology and metabolism were reviewed [1831]; studies of the distribution of radioactive gold injected as the colloidal metal [1819] and of gold chloride [a highly toxic gold salt, not used clinically—Ed.] by histochemical methods [495] largely confirmed previous observations (see Ninth Rheumatism Review). Biopsies of various tissues from a patient with rheumatoid arthritis who had received radioactive gold as gold sodium thiosulfate indicated a much greater concentration in the synovial membrane and fluid than in muscle, fascia or skin.[143] [Subsequent studies indicate a tendency for gold to be accumulated in several types of inflammatory tissue.—Ed.]

A review of various hypotheses to explain how gold exerted its action in rheumatoid arthritis indicated none which seemed helpful.[1831] Its failure to protect guinea pigs against lethal doses of histamine or against anaphylaxis, and absence of an effect on Arthus' phenomenon in rabbits, did not suggest an anti-allergic action.[1151] In four cases of hepatitis presumably due to gold toxicity, two had temporary improvement in arthritic symptoms concomitant with the jaundice but none developed remissions, which did not support the theory that gold salts produce their beneficial effect by injuring the liver.[801] The effectiveness of BAL in gold toxicity and the ability of this thiol compound to reactivate sulfhydryl enzyme systems led again to the suggestion that gold compounds may exert their therapeutic effect by changing tissue enzyme reactions.[1625] In vitro studies on rat tissues of the effect of thiol compounds on the inhibition of oxygen uptake which is produced by gold compounds failed to support this concept, but added little to an understanding of the mode of action of gold. Results suggested the possibility "that the empiric development of therapeutic gold preparations has already taken advantage of the thiol detoxification mechanism." [162]

Dosage and Methods of Administration. The majority of gold compounds used in America have a metallic gold content of approximately 50 per cent (gold sodium and gold calcium thiomalate, gold thioglucose and gold thioglycolanilide); gold sodium thiosulfate contains only 37 per cent gold, so if this preparation is used the dosage should be gauged according to the actual amount of gold injected.[172]

In recent years the trend has been toward smaller individual doses, not to exceed 50 mg. of a soluble gold compound or 25 mg. of actual gold. The dosage plan advocated by most authorities [236, 297, 317, 601, 844, 1624, 1645, 2000] is as follows: first dose, 10 mg. intramuscularly; second dose, 25 mg.; third and succeeding doses, 50 mg. An interval of one week is usually allowed between injections. Some preferred to give individual doses of 25 mg. once a week.[1820]

Whereas an arbitrary maximal dose may be adhered to, dosage should be regulated somewhat according to the patient's response and the development of toxic symptoms.[1069] In mild cases, and in those suspected of being drug-sensitive, individual doses of 25 mg. probably should not be exceeded. In stubborn cases, doses up to 100 mg. may be permissible if the patient is willing to take the risk involved, but usually the larger amounts will also be disappointing.[295]

Most authors [236, 297, 317, 1624, 2000] agreed that the total quantity administered in a course should be between 750 and 1,500 mg. of a soluble salt (375 to 750 mg. of metallic gold). But according to Cecil [295] there should be no fixed limit, because some patients improved rapidly and needed comparatively small amounts, while others were resistant and needed larger total quantities. Ragan and Tyson [1632] contended that if no response is obtained after 2,000 mg. are given, further use of gold will bring about no improvement.

Formerly the popular treatment schedule was to give one, two or several courses of gold therapy with rest intervals of six weeks to six months between courses. The modern trend has been to administer a single course, followed thereafter by "maintenance doses" consisting of 50 mg. every two to four weeks for an indefinite period.[236, 295, 297, 317, 1624, 1631] The purpose of the maintenance dose plan is to reduce the incidence of relapses.[598]

Results of Chrysotherapy. Both immediate response and results after three to four years were reported in 142 patients (72 received gold sodium thiomalate; 19, gold calcium thiomalate; and 51, gold thioglucose). The immediate response after a single course of 0.5 gm. or more was: marked subjective improvement in 55 per cent with marked objective improvement in 50 per cent; no improvement in 11 per cent; definite but "not startling" improvement in the others. Thirteen per cent remained asymptomatic for 45 to 78 months after a single course. Seventy-five per cent relapsed; of those who relapsed and received a second course of treatment, 80 per cent again obtained improvement.[1632] Results were summarized in these general terms: of patients receiving full treatment with one or two courses, 10 to 20 per cent can be expected to show no improvement, and 40 to 60 per cent to show striking improvement; but 80 to 90 per cent of these can be expected to relapse within five years, with 80 per cent of these again being benefited by gold.[317, 1624] Other workers gave a total of 721 courses of gold thioglucose to 475 patients and reported that 90 per cent of the patients showed either subjective or objective improvement and that 64 per cent demonstrated definite objective improvement.[327] Using gold sodium thiosulfate, remission or great improvement was obtained in 51.4 per cent of 455 cases. In contrast, only 15 per cent of a control group receiving various measures other than gold improved. Of 116 improved cases followed for five years, 57 per cent relapsed, and of 32 patients followed for 10 years, 75 per cent had relapsed.[1121] "Favorable therapeutic response" was reported in 90 per cent of 150 patients treated with sulfhydryl gold naphthyltrisulpho-carbonium (Aurocein).[1512] Freyberg [598] compiled statistics on therapeutic results of 4,086 cases which appeared

in the European and American literature between 1935 and 1948; 61 per cent were reported as arrested or greatly improved.

Adams and Cecil [8] compared results in 106 patients who received gold sodium thiomalate or gold thioglucose during the first year of their illness with those obtained in a control group of 83 patients who were treated by conventional methods without gold. All patients were under observation for a minimal period of one year after optimal therapeutic effect was obtained, and for total periods ranging from 18 months to 12 years. One year after institution of treatment, remissions had occurred in 66 per cent of the gold-treated patients and in 24.1 per cent of the control group. Remissions were noted 10 months sooner in the gold-treated cases than in the controls, the average figures being 7.1 months versus 17.1 months. The incidence of "complete" remissions was 44.8 per cent in the gold group, as compared with 27.7 per cent in the controls. The relapse rate was 26.1 per cent for the gold treated remissions, 33.3 per cent for the control remissions. They concluded that gold salts, if administered during the first year of rheumatoid arthritis, increase and accelerate the appearance of remissions.

The findings of others were less favorable. Short, Beckman and Bauer compared their results in 35 patients given a single course of chrysotherapy with those of 274 cases receiving only general and orthopedic treatment. Of the 35 cases receiving gold, 21 (60 per cent) obtained immediate improvement, but 13 later relapsed, giving a total new improvement in only eight cases (23 per cent). Better net results were claimed from general measures alone, 52.9 per cent showing improvement.[1831] Forty-seven patients, all receiving soluble gold preparations in total amounts ranging from 500 to 3,000 mg., were observed for periods of 18 months to six years. Only 23 per cent maintained an improved state after treatment, 62 per cent showed no appreciable change, and 15 per cent became worse.[230]

The results of "maintenance dose" therapy in 58 patients were compared with those in 62 control patients receiving general supportive treatment only. The patients treated with gold sodium thiosulfate or gold thioglucose received an average total dose of 3,200 mg. (1,600 mg. in terms of the metal). Results of chrysotherapy vs. control group were as follows: arrested, 20.7 vs. 9.7 per cent; markedly improved, 36.2 vs. 19.4 per cent; improved, 24.1 vs. 27.4 per cent; unimproved, 19 vs. 43.5 per cent.[2101]

Using an insoluble compound, gold thioglycolanilide (Lauron), improvement was claimed in 73 per cent of 100 cases,[1690] and in 73 per cent of 91 cases.[1718] Others used the same preparation in massive doses (0.9 to 10 gm. given intramuscularly in divided doses within a six to eight week period) in 18 cases. Intensive therapy offered no advantage over usual treatment with lesser doses.[606] Pellets containing 850 to 865 mg. of gold thioglycolanilide were implanted either subcutaneously or intramuscularly in six patients with the hope that this method might be effectively substituted for repeated injections; clinical results were inconclusive and a foreign-body type of reaction developed in one-half of the cases.[1291]

Relapses. When a course of gold is given and therapy is then discontinued, the incidence of relapse is high: from 50 to 80 per cent.[297, 317, 1624, 1831] Although patients may receive further benefit from more gold, the results from a second course are not likely to be as good as from the first. Relapses were noted to

occur just as often among early as among late cases, and were more likely to occur if the patient returned to fairly strenuous physical work.[844] The relapse rate with patients receiving "maintenance doses" of gold appeared to be significantly less[2101] [but adequate data are lacking.—Ed.]

Toxic Reactions. The hazards attending the administration of gold salts are a great drawback to their use. The incidence of toxic reactions in recent reports ranged from a low of 4.6 per cent[1512] to a high of 62 per cent.[236] This wide variation probably depends on several factors, including the gold preparation used, the dosage employed, the caution exerted during therapy, and consideration of what reactions are worthy of note. Most agree that about one patient in four experiences some untoward effect, the majority of these being minor.[1821] Ragan and Tyson[1822] noted signs of toxicity (pruritus, rash, stomatitis or blood dyscrasia lasting more than a month) in 39 per cent of patients receiving gold sodium thiomalate, in 31 per cent of those receiving gold thioglucose, and in 21 per cent of those receiving gold calcium thiomalate. Minor reactions, including skin rash, mouth sores and transient albuminuria, developed in about 25 per cent of Cecil's cases.[295] Serious reactions such as exfoliative dermatitis, hepatitis,[808] ulcerative enterocolitis, thrombocytopenic purpura,[1378] leukopenia, agranulocytosis, aplastic anemia and encephalitis are not common, although accurate figures are not available. In two series, death occurred in two of 460 cases[1632] and in two of 600 cases.[1624] Mortality, reported to be as high as 3 per cent in 1935, fell to approximately 0.4 per cent for the period 1939 to 1945. The lessened mortality has apparently resulted from: (1) employment of smaller doses; (2) better knowledge of gold metabolism, its clinical effects and signs of toxicity; (3) better clinical and laboratory precautions, and (4) improved treatment of toxicity, recently by means of 2,3-dimercaptopropanol (British anti-lewisite, BAL).[598, 641]

Prevention and Treatment of Toxic Reactions. The physician must be ever watchful for early signs of intolerance. The patient should be questioned at each weekly visit and the skin and mouth examined for reactions. A complete blood count and urinalysis should be made at least once a month, or oftener if the possibility of untoward reaction is suspected.[170, 297, 1624] Allergic individuals should be followed with particular care.[295] Mild albuminuria was considered a sign for caution, not for discontinuance of therapy[1069, 1071]; but with signs of active renal irritation (albuminuria of 2 plus or more, red cells or casts in the urine, or an increased blood urea nitrogen), gold should be discontinued permanently.[295] Some considered eosinophilia a sign of poisoning,[1820] and basophilic stippling of erythrocytes a frequent indication.[1532] There was no sure way to detect impending dermatitis; eosinophilia was not necessarily indicative,[844, 1666] but pruritus often preceded skin lesions. Increased menstrual flow sometimes foreshadowed a lowered platelet count and impending hemorrhagic purpura.[1645] Although there were no sure ways of preventing toxic reactions, small doses and constant vigilance allowed therapy to be carried out with a fair degree of safety (Cecil).

British anti-lewisite (BAL) (2,3-dimercaptopropanol) has proved effective in controlling some of the serious reactions.[482, 1149, 1278, 1440, 1692] Ragan and Boots[1625] used the drug in five patients with severe gold dermatitis; in four the pruritus and rash cleared up promptly, but in one case with long-standing dermatitis the treatment was ineffective. In all five patients there was enhanced urinary excretion of gold coincident with the administration of the drug; within a month four of the patients experienced exacerbations of articular symptoms. Favorable responses of dermatitis were reported also by others.[328, 402, 1410, 1645] The use of BAL resulted in spectacular recovery in a case of thrombopenic purpura and in one of agranulocytosis,[1230] but failed in a case of aplastic anemia.[557] BAL was found to protect rats against lethal doses of gold sodium thiosulfate given intramuscularly and to expedite excretion of

the metal.[1156] Unfortunately, BAL is not an ideal antidote because it may produce reactions of its own,[328, 1725] and may itself cause skin sensitization.[1419]

Penicillin, acting as a temporary substitute for the phagocytic activity of granulocytes while granulopoiesis is being resumed, is an important adjuvant in the treatment of agranulocytosis; a case resulting from chrysotherapy was successfully treated.[181] Good results in three cases of hemorrhagic purpura were obtained with blood transfusions and large daily doses of vitamin K.[1645] [Prompt and effective control of severe dermatitis and of thrombocytopenia resulting from chrysotherapy has more recently been obtained with cortisone and corticotropin.—Ed.]

Conclusions on Chrysotherapy. Gold compounds cannot be regarded as constantly effective agents for the treatment of rheumatoid arthritis, but before the advent of cortisone and corticotropin their advocates claimed that no other form of therapy was capable of altering favorably the course of the disease in such a high percentage of cases.[297, 317, 1071, 1690, 2101] [The availability of cortisone and corticotropin has not led to an abandonment of chrysotherapy; some workers recently have suggested that the use of gold compounds and hormones can be advantageously combined. The case for chrysotherapy now should be r.o better and no worse than it was B. C. (before cortisone).—Ed.]

Because of the high percentage of toxic reactions attending their use, gold compounds are far from satisfactory therapeutic agents.[2101] Some asserted that results from older and more conservative methods are "as good as or better than gold," and expected gold compounds to be abandoned even though no new substitute should appear on the horizon. Several authors[106, 311, 1831] believed that the case for gold therapy is unproved as a palliative or adjuvant measure, and that the hazards attending it should furnish a decisive argument against its general use. Advocates of gold therapy admit that it should not be relied on exclusively, and that it should be used in conjunction with general measures (rest, salicylates, nutritious diet, physical therapy, etc.). But in view of the serious potentialities of rheumatoid arthritis, many agree with Hench[844] that chrysotherapy, although still on trial, is justified whenever rheumatoid arthritis has lasted more than a few months and shows evidence of being progressive, provided that the patient understands and is willing to share the risks involved.

Sulfonamides. These have been found useless for rheumatoid arthritis.[172, 1067] However, Parr and Shipton[1533] used sulfadiazine and sulfaguanidine over long periods in 43 cases and asserted that 22 were "cured," 17 improved and four unimproved. Since 1941 Svartz, in several publications, has contended that Salazopyrin (a combination of salicylic acid and sulfapyridine) is effective in the treatment of "rheumatic polyarthritis." Other investigators have not been able to confirm these observations, but Kuzell and Gardner[1153] believed that 14 of 30 patients were relieved symptomatically by its administration. However, Sinclair and Duthie,[1853] in a well controlled study, tested the effects of the drug in 20 patients with rheumatoid arthritis and concluded that it was worthless.

Antibiotics. Antibiotic agents have proved ineffective in the hands of most investigators,[172, 761, 1067] but a few favorable reports have confused the issue. Large doses of penicillin were given intramuscularly daily for from three to six weeks, or orally for from one to six months, without benefit.[148, 257, 844] Streptomycin in total doses of 10 gm. over a period of five to six days, and larger total quantities ranging from 25 to 80 gm. (at a rate of 4 gm. daily), failed to alter the disease.[1073] Working on the hypothesis that pleuropneumonia-like organisms might be harbored by the rheumatoid patient and serve as a persistent antigen, Brown and co-workers[234] admin-

istered aureomycin (1.0 to 2.5 gm. a day) to 13 patients with peripheral rheumatoid arthritis for periods ranging from four to 16 weeks. Their results were reported as follows: complete remission in two, major improvement in seven, minor improvement in two, and no improvement in two. On the other hand, Kuzell et al.[1134] found aureomycin to be ineffective in the treatment of patients with rheumatoid arthritis. One physician [712] reported that 21 of 24 patients were relieved of joint pain (30 to 100 per cent) by taking small doses of chloromycetin [but added that the "work was done rather haphazardly during the course of a busy office practice" and that most of the cases were "followed in retrospect."—Ed.]

Antispasmodics. In 1944 Trommer and Cohen reported marked relief from pain and relaxation of muscle spasm in 16 of 19 patients given neostigmine bromide by mouth. Subsequently they claimed even better results with physostigmine salicylate (0.6 mg. to 1.2 mg. per dose) given subcutaneously. Improvement of muscle spasm was noted in 120 of 153 patients; deformities were thought to be prevented and sometimes decreased if already formed.[330] Similar claims were made by others.[1918, 2222] But a careful study yielded essentially negative results. Prostigmine was given to the limits of tolerance by both subcutaneous and oral routes to 23 patients with rheumatoid arthritis; appreciable decrease in muscle spasm occurred in only two, consistently in only one. Unpleasant and often alarming reactions occurred in 14 of the 23 cases.[80] Rawls and associates used prostigmine in over 1,000 cases, and the number showing improvement was "relatively small." [1645] In 20 cases treated with subcutaneous neostigmine methylsulfate, the drug was found to have an inconstant and irregular effect on pain and range of motion in 13; no objective effects on the joints, general health, or sedimentation rate were noted.[1250] Curare (*d*-tubocurarine in oil and wax) was tried in a number of rheumatic disorders associated with muscle spasm. In 23 patients with rheumatoid arthritis, three to six injections of 175 units (1.0 c.c.) of the preparation were given at intervals of every two to three days; none of the patients displayed clinical evidence of improvement, subjective or objective.[1292]

Antireticular Cytotoxic Serum (A.C.S.). Further experience has substantiated Bach's conclusions (1945) that A.C.S. was probably worthless in the treatment of rheumatoid arthritis.[188,1645] Twenty patients were treated, with inconclusive results.[1624] Of 29 patients, 23 were unchanged or worse following treatment; improvement in the remaining six cases was questionable.[601, 1711] Of 30 patients who received the serum, one was moderately improved, four were slightly improved, 16 were not improved, and nine were worse.[1120]

Spinal Pumping. Working on the assumption that rheumatoid arthritis is a neuropathic disorder, Speransky (1935) treated 15 cases by pumping spinal fluid in and out of the subarachnoid space, thereby inducing shock to the central nervous system. Recovery was reported in four cases, improvement in nine, and no change in two. This curious form of treatment was tried by Gillman and Gillman [644] in 70 patients; 12 had acute rheumatic fever, 36 had "subacute arthritis" and 22 had "chronic arthritis." [From descriptions given, probably all of the 36 subacute and the 22 chronic cases had rheumatoid arthritis.—Ed.] Of these 58 cases, 28 were reported as recovered, 16 as improved (five relapsed later), and 14 as unchanged. Others were even more enthusiastic, and stated that of 10 patients subjected to the procedure, eight recovered and two improved.[22] However, the results of more critical investigators [194, 1761] failed to substantiate these claims or to justify the use of such a radical and unorthodox "treatment." [Spinal pumping evidently disturbs the central nervous system and results in a widespread influence on the peripheral vascular system; severe sweating, rise in skin temperature, capillary dilation and pulsation in the ocular fundi, and fever (from 1 to 5 degrees in more than one third of cases) are induced. One fatal case demonstrated, at necropsy, severe occipital and frontal hemorrhages and petechial hemorrhages scattered throughout the rest of the brain.—Ed.]

Salts of Heavy Metals Other Than Gold. One report [1836] claimed that bismuth tartrate was as effective as gold salts; 36 of 40 patients given injections of bismuth were said to have "improved." [Details of results, criteria of improvement and controlled studies were lacking. These results have not been confirmed by one of us, C. R.—Ed.] Forestier [578] contended that copper salts were effective in the treatment of rheumatoid arthritis and that they gave better results than gold salts in early cases. In 17 early cases given either Cupralene (M'(allyl-cuprothiourea)sodium benzoate) or Dicuprene (cupro-oxyquinoline-diethyl sulfonate), no therapeutic failures were observed. Gold salts were preferred for cases of longer standing. These observations were not confirmed in a study of 27 patients (including seven in the first year of the disease) treated with Cupralene. Only two experienced temporary remission, a number "proportionate to the per cent of spontaneous remission observed with no specific treatment." [2078] [Cupralene was also ineffective in 10 cases treated by one of us, W. G.—Ed.]

Trials with Other Substances. Sulfur therapy still had advocates: Libenson and Wittenborn [1217] believed that sodium tetrathiodiglycollate (Anathion), a substance thought to release sulfur at the tissue level, was highly effective in 25 patients with rheumatoid arthritis. [The preparation appeared ineffective to one of us, C. R.—Ed.] Marked improvement or complete recovery was claimed in 66 per cent of 144 rheumatoid arthritic patients treated with adenosinetriphosphoric acid (ATP); only 14.6 per cent failed to show some response.[279] Kersley and Simpson [1077] found calcium ortho-iodoxybenzoate totally ineffective. Results were equivocal with glucuronic acid administered orally.[898] [In the hands of others, results were nil.—Ed.] Aluminum subacetate proved ineffective; 11 of 12 patients with rheumatoid arthritis given the preparation orally for periods of from one to two years failed to improve, and recalcification of osteoporotic bones did not ensue.[159a] Para-aminosalicylic acid was tried in six cases of rheumatoid arthritis without beneficial results; toxic symptoms were troublesome and varying degrees of hypoprothrombinemia were noted in each case.[408] Six patients with active and progressive rheumatoid arthritis were given therapeutic trials with diamidine and stilbamidine; results were negative.[1723] Two patients with peripheral rheumatoid arthritis were treated with injections of Thorium X and reported as improved.[869] Varying degrees of improvement in 264 of 292 cases were claimed to have resulted from administration of intestinal mucosa rich in erepsin (enteric-coated capsules).[1688]

Physical Therapy. Most rheumatologists consider physical therapy as a necessary adjunct to successful management [297, 515, 761, 1078, 1516, 1585, 1855, 2001, 2107]; it helps the ship to "weather the blow" so that there is less wreckage when the storm clears.[1549] Home regimens consisting of simple measures often suffice.[601, 1063, 1820, 2066] Local heating of large joints may be carried out with a simple home-made luminous baker, clamp lamp, wet packs, or applications of paraffin wax; contrast baths, paraffin dips, or home whirlpool baths are useful for hands or feet; thermal tub baths each morning are helpful; massage can usually be provided if a member of the patient's family is instructed in a few simple strokes; and active, passive and resistive exercises can be carried out adequately at home.[1063, 1260] Supplementary treatments performed by a skilled technician once or twice a week are often advisable.

It is assumed that increased blood flow hastens resolution of inflammation by maintaining adequate amounts of oxygen and nutritional materials for the metabolic needs of involved tissues; thus benefits derived from heat depend on the frequency and duration of peripheral vasodilatation. By testing skin temperatures with various types of heat applications, the degree and length of vasodilatation were found to be much the same whether the heat was moist or dry. General body heating (body baker, fever

cabinet, Hubbard tank) resulted in more prolonged elevations of skin temperatures (feet and hands) than did local applications of heat. The type of systemic heating apparatus used was immaterial; a simple home-made luminous body baker or hot tub bath was as efficacious as others.[1301] Some considered ion transfer with vasodilating drugs, histamine and acetyl-β-methyl-choline of value in providing local relief when other measures failed.[1130] But local heat applications are usually adequate, more practical, less expensive and simpler.[1078]

By employing the venous occlusion plethysmograph with a compensating spirometer recorder, the influence of contrast baths on blood flow was determined. The greatest increase in blood flow was obtained when all four extremities were treated simultaneously, and significant vasodilatation persisted at least 45 minutes after contrast baths to four extremities simultaneously.[507] Hollander and Horvath[911] used various physical therapy measures while testing skin and intra-articular temperature changes simultaneously. The intra-articular temperature was increased only slightly by immersion of the joint in hot water or by passive motion, was increased somewhat more by radiant heat and the application of paraffin to the surface, and was increased most when high frequency electrical energy was employed.

Artificial hyperpyrexia induced by the Kettering hypertherm or an electromagnetic apparatus, with temperature maintained at 104° to 106° F. for several hours, has been almost entirely discarded.[172, 1725] The procedure is exhausting, sometimes harmful, and at best relief is temporary. Temperature elevations to 100° or 101° F. for 30 minutes may be used advantageously in some cases[1078]; but these may be produced just as efficiently with hot tub baths or luminous body bakers.[170, 1301]

Since rheumatoid arthritic joints are already inflamed, massage must be gentle and carried out in the neighborhood of, but not immediately over, affected joints.[1130] Massage of the extremities produced some rise of cutaneous temperature, but of shorter duration than that obtained from any form of heating.[1301] [Often too much emphasis is placed on massage, as if it had some supernatural healing power. Its chief value is in preparation for therapeutic exercises.—Ed.]

Therapeutic exercises are best performed following local heating and massage.[1063] They have as their objects: (1) to preserve the function of joints; (2) to maintain the tone of muscles; (3) to prevent and overcome contractures and deformities.[297, 883] But exercises should be chosen with discrimination and performed slowly and rhythmically.[1221] They should be graduated from passive to active assistive, and finally to active voluntary movements, depending on the degree of joint inflammation.[908] In subacute cases it is safer to begin with passive joint motions, gradually extending them to the fullest possible range[1130]; one slow daily movement through the fullest possible range of motion in each direction is preferable to many minor movements through a partial range.[1063] Underwater exercises often allow a greater range of painless motion. Active exercises should be started as soon as possible; for bed patients, muscle setting and postural maneuvers are indispensable.[1585] Technics of pulley exercises for stretching various joints and increasing muscle strength were described,[409] mechanical devices for mobilizing joints were illustrated,[575, 1472, 1858] and useful home exercises for correcting and preventing deformities were outlined.[908]

Occupational Therapy. Intelligently directed occupational therapy can be an important adjunct in treatment.[369, 726, 1187, 2224] It not only serves diversional and vocational purposes, but also may be utilized to increase the activity of involved joints. A stationary bicycle may be used for ankles, hips or knees; a sewing machine for ankles; clay modeling or hammering for fingers or wrists; basket-making or loom-

weaving for shoulders, elbows and upper back.[214, 1062] Crafts requiring cramped and repeated small movements of fingers should be avoided.[421]

Spa Therapy. The modern health resort is a place where patients may be benefited by physical therapy, rest, climate and relief from socio-psychosomatic influences [51] but no spa treatment method has any specific effect on any form of rheumatism.[1130] The exertion of taking treatments in a spa, especially from too intense heating, may sometimes be more detrimental than the possible benefit to be derived.[1130]

Climate. Many patients with rheumatoid arthritis live more comfortably and sometimes the disease responds better when they are transferred to a warm dry climate,[297, 317, 341, 1130] but a change of residence should be suggested only if financial hardships will not develop and if serious dislocation of family relationships will not follow.[1621]

Edström and co-workers [483] continued their studies in the climatic laboratories at Lund, Sweden. β-hemolytic streptococci were present in the throat flora of most patients on admission to the dry hot rooms, and they usually disappeared during the stay. Clinical improvement in the manifestations of rheumatoid arthritis (lessening of periarticular and capsular swelling, reduction of pain and joint contractures, increased appetite, and disappearance of the blue-livid coloration of skin on hands and feet) were frequently noted.

Nonsurgical Orthopedic Measures. The prevention of deformities demands constant alertness by both the physician and the patient.[1082] The insidious development of such deformities as deviations of the fingers at the metacarpophalangeal joints, flexion contractures of the knees, wrists and hips, adduction contractures of the shoulders and pronation of the feet are to be watched for particularly.[1058] Major deformities can usually be prevented by the application of simple plaster of Paris or moldable aluminum splints; these are most satisfactory when they are "tailor-made" on the patient.[1043, 1058] Optimal positions for rest and splintage were listed by Capener.[274] Splinted joints must be moved through their full range of motion at least once daily to prevent the development of adhesions.[101] Orthopedic appliances for correcting deformities of various joints were described.[83, 274, 480, 629, 1258, 2045]

Flexion contractures of knees should be corrected early. Traction may accomplish this in a few patients, but more forceful means are often needed.[601] Manipulation under anesthesia has little place in the treatment of rheumatoid arthritis [1082, 1367]; fresh adhesions usually form quickly to restore the joint stiffness and deformity (Key), and the procedure is dangerous because atrophic bones are apt to be fractured.[1082]

Surgical Orthopedic Measures. Synovectomy has no established place in the treatment of rheumatoid arthritis, but some considered it a useful procedure for large boggy knees resistant to other forms of therapy.[101, 1082, 1524] The synovial membrane is no longer removed under the mistaken idea that it may be a focus of infection. Poor results can usually be attributed to the development of adhesions, which tend to form quickly if motion is not started soon. To prevent adhesions Kuhns and Potter [1141] recommended the interposition of nylon membrane. Posterior capsulotomy is a valuable procedure for fixed flexion contractures of knees; results are best when cartilaginous damage is minimal.[101]

Arthrodesis is rarely advised for rheumatoid arthritic joints,[83] but occasionally the operation may be justified to relieve pain rapidly at a knee or hip joint.[1183] Severely damaged joints usually develop fibrous or bony ankylosis in the course of the disease, and the physician's task is to keep the extremity in good weight-bearing posi-

tion until fusion takes place.[1140] While arthroplasties have been described for most major joints, useful joints have been obtained by this procedure chiefly at the elbow, hip and knee.[83] Well-fitting articular surfaces can usually be formed without difficulty, but the bones may not remain as they have been shaped; upon weight-bearing and motion the reconstructed bone-ends tend to become distorted. The distortion is less when plastic or metallic molds are fitted over the articular surfaces.[1163] When ankylosis has taken place at the hip joint, arthroplasty may be indicated if the patient must sit for work. In persons who must stand, a stiff, painless hip in a good weight-bearing position is usually more satisfactory.[1140] Partial denervation of the hip for relief of pain in various types of chronic arthritis, while more suited for osteoarthritic hips, provided satisfactory relief in four of five painful hips due to rheumatoid arthritis.[1492]

Sympathectomy can be depended upon to increase heat and to decrease sweating in an extremity, but it probably has no effect on the course of rheumatoid arthritis; the operation has been almost entirely abandoned.[1082]

Course and Prognosis of Rheumatoid Arthritis

It is well established that the natural course of rheumatoid arthritis is characterized by periods of exacerbation and improvement. It is less generally known, however, that the disease often becomes arrested and that some patients may recover completely. Efforts to gather long-term prognostic data are handicapped because most patients have received some form of treatment which may influence the natural course of the disease.[174] It therefore becomes necessary to rely for such information on groups of patients whose treatment has been confined to simple, nonspecific measures, or to measures which have been proved of doubtful value. Short and Bauer[1832] reported long-term observations on such a group of 250 unselected patients whose treatment was limited chiefly to rest, simple analgesics, adequate diet with supplementary vitamins, physiotherapy, and orthopedic procedures when indicated. In addition, a minority of the patients had received fever therapy and treatment of infectious foci. The duration of observation varied between six months and 16 years, with an average of 9.6 years; 80 per cent had been observed five years or longer.

At the time of the progress report, improvement was observed in 133 patients (53 per cent), 38 of whom were in complete remission (15 per cent of the total group). The disease was stationary in 32 (13 per cent) and worse in 85 (34 per cent). Only 38 patients, or 15 per cent, were confined to bed or wheel chair. These figures indicate that the prognosis is by no means as unfavorable as is often supposed. Worthy of emphasis is the predominance (66 per cent) of those patients who after several years' illness were either improved or essentially unchanged despite lack of "specific" therapy.

In the same study, the most striking factor affecting prognosis was found to be the duration of the disease prior to initial observation. The outcome was most favorable among patients seen within the first six months of their illness: 81 per cent of such patients later improved; in those patients whose onset dated back more than one year, the outcome was not related to the duration of the disease. Male patients without spondylitis, patients under 40 years of age, those with asymmetrical joint involvement and those with mild involvement had more favorable outcomes. Nearly one-half of patients showing significant improvement had relapses of the disease later.

Factors of no apparent importance in determining a patient's course included

anemia, history of prodromal symptoms before onset, an intermittent rather than a progressive course prior to initial observation, an acute onset rather than a gradual one, family history of rheumatoid arthritis or rheumatic fever and, in women, onset within two years before or after the menopause.[1832] Other workers concluded that the presence of subcutaneous nodules was of no prognostic significance in rheumatoid arthritis.[1251]

[Despite these interesting and important prognostic observations, it unfortunately remains impossible to predict in the individual patient the course of his disease. In a patient with a mild disease, a severe relapse may occur without warning at any time, while the most malignant example of the disease may suddenly become arrested.—Ed.]

Polley [1585] believed that the course of rheumatoid arthritis can be modified in most instances, and that the response is fairly prompt and satisfactory in 25 per cent; improvement of varying degree with ultimate subsidence of the disease occurs in 50 per cent; and the response is unsatisfactory in only 25 per cent of cases. Steiner, Freund, Leichtenritt and Maun [1951] warned against optimism to the point of pronouncing a "cure." They found microscopic evidence of active inflammatory foci in muscles and nerves of patients whose disease clinically was supposedly "burnt out," and they wrote: "Rheumatoid arthritis, even in its late stages, is not a disease which has terminated in scar formation, but is a smoldering, active, distinctive entity as shown by the presence of inflammatory foci in the muscles and perineurium."

Rheumatoid (Ankylosing) Spondylitis

The incidence was estimated at one per 2,000 of the general population.[2158] Distribution is worldwide; it has been observed in every climate. Following both World Wars, incidence of spondylitis was apparently increased, but segregation of young men was doubtless responsible at least in part for this apparent increase. Strenuous activities and adverse living conditions in the military services brought to light many mild and early cases, previously undiagnosed.[171, 1642, 2158]

Male patients again predominated in all series, but in varying ratios. Most writers reported that 90 per cent, or more, of all patients were male.[171, 272, 367, 695, 858, 1148, 1190, 1605, 1851] Of 1,035 persons with rheumatoid spondylitis studied at the Mayo Clinic between 1935 and 1943, 931 were male (90 per cent).[858] In another series 60 per cent of the patients were male.[559] It was suggested that the "psychodynamics of increased muscle tension in men in the presence of cultural taboos against passivity may be an etiologic factor in their predilection for rheumatoid arthritis of the spine."[1884] Young athletic individuals were usually affected during the period of life before degenerative changes set in,[1190, 2158] but initial symptoms may occur at any age: in the Mayo Clinic series they occurred in persons from four to 63 years old, the average being 27 years. Rheumatoid spondylitis was observed in 17 children (11 girls and six boys) all under 10 years of age.[1252] The cause remains unknown. Opinion remained divided as to whether this condition is a variant of rheumatoid arthritis or a separate disease. Both affirmative [858, 1184, 1190] and negative [76, 807, 1148, 1184, 1444, 2172] views were presented.

The pattern of inheritance of this disease was observed in 50 families; after analysis of pedigrees and statistical tests on pooled data, it was concluded that ankylosing spondylitis could be attributed to an autosomal dominant factor, with about 70 per cent penetrance in the male and about 10 per cent penetrance in

the female.[872] Ankylosing spondylitis was reported in two pairs of fraternal twins[272, 1710] and in sisters.[585]

Clinical Data. Symptoms and signs of rheumatoid spondylitis were reviewed.[76, 171, 559, 695, 807, 858, 1148, 1190, 1444, 1531, 1588, 1927, 2025, 2158] Symptoms at onset varied from mild or trivial pain and stiffness to severe attacks of low-back pain and sciatica. Lumbosacral pain was frequent, sometimes extending into one or both buttocks or to posterior aspects of one or both thighs. Pain sometimes first appeared in either the upper lumbar, midthoracic or cervical region. A feeling of tightness or stiffness of the chest was not unusual, and sometimes preceded back pain. Associated muscle stiffness was the rule, especially notable in the morning or after periods of inactivity, and usually relieved by physical activity and heat. Severity of symptoms as well as the clinical course varied greatly. Remissions may occur at any time, and progress of the disease may apparently be halted temporarily by therapeutic measures.

On examination, impaired flexion of the spine, diminished thoracic expansion and reduced vital capacity were usually noted. Hips and shoulders were occasionally involved; in some cases tenderness and swelling were noted over the sternoclavicular and manubriosternal joints. Costochondral cartilages were tender in some patients.[807] Iridocyclitis often preceded back symptoms,[807, 1190, 1444, 2158] and occurred as a complication in 11.4 per cent of one group of 1,035 patients.[858]

Tenderness over ischial tuberosities was a frequent complaint in one series, sometimes accompanied by rarefaction of bone and periosteal reaction, with calcification of tendons at their insertion into the ischial tuberosities.[807, 1444] Frequently a painful point was found on the plantar surface of the *os calcis*, and pain in the heels could be either acute or chronic.[400]

In 352 patients (292 males and 60 females) suffering from ankylosing spondylitis, clinical evidence of heart disease was detected in only 16 patients (4.5 per cent). Aortic insufficiency was found in six, associated with aortic stenosis in three. Mitral stenosis was detected in four, and was combined with aortic insufficiency in two. Heart block, pericarditis and auricular fibrillation without valvular defects each were found in two patients. Electrocardiograms were abnormal in 47 of 190 instances (24 per cent). Conduction time was prolonged in 29 (15 per cent). A history suggestive of acute rheumatic fever was obtained twice as often as in controls.[139]

Laboratory Data. Increased sedimentation rates and mild hypochromic anemia are well known features of rheumatoid spondylitis. However, sedimentation rates were normal in nearly one fifth of a large series,[1588] and in general were somewhat lower than in peripheral rheumatoid arthritis. "Practically all patients" showed normal values for acid and alkaline phosphatase.[422] Changes in serum proteins (decrease in albumin and increase in globulin values) were similar to those observed in rheumatoid arthritis.[807] Serum flocculation reactions (combined thymol test) were negative, in contrast to positive reactions in more than half of 26 patients with rheumatoid arthritis.[1444] Colloidal gold reactions of serum were generally negative. Increased urinary excretion of 17-ketosteroids was reported in both men and women with rheumatoid spondylitis.[404, 404a] Other reports failed to confirm this finding.[423, 807, 1444]

Spinal Fluid. Cell counts, manometric pressures and concentrations of glucose were normal in 50 patients; protein levels were increased in 21, ranging from 47 to 98 mg. per 100 c.c. The magnitude of this increase appeared related more to the severity than to the duration of the disease.[422]

Roentgenograms. Frequently roentgenograms are the means of arriving at a correct diagnosis of this condition.[1604a] Roentgenographic changes may be apparent before symptoms are experienced, but the reverse is also true. Sacroiliac joints usually are the first sites of roentgenographic changes; however, this disease may be present with negative roentgenographic findings.[1148, 1531, 1588] [The diagnosis of rheumatoid spondylitis in the absence of roentgenographic proof can be presumptive only. Such patients should be followed by serial x-ray examinations to establish or disprove the diagnosis.—Ed.]

Severity of the disease may be reflected by the character of x-ray changes in the sacroiliac joints. Lapse of time between onset of symptoms and appearance of ankylosis in sacroiliac joints may vary widely in different individuals. In one study this period ranged from two years in one instance to more than 15 years in another.[183] Absence of roentgenologic involvement of sacroiliac joints [distinctly unusual—Ed.] was observed in nine instances among 1,035 cases. Involvement of only one sacroiliac joint was observed in only six.[1588] [Experience has shown that unilateral sacroiliac arthritis may prove to be due to a specific infection, such as tuberculosis, or may represent an early stage of rheumatoid spondylitis.—Ed.]

Forestier's classic description of the roentgen findings was reviewed. In the first stage, "pseudo-widening" of the lower segment of one or both sacroiliac joints may be noted. Adjacent bone appears "hazy" and the joint line fades on the iliac side. Subsequently, bone density is decreased. After a period of months or several years the second stage is recognizable by mottling of cancellous bone adjacent to the joint, in both the ilium and the sacrum. Some areas are translucent, others appear unusually dense. In the third and last stage the joint space is lost and synostosis results. Bone is more uniformly dense, and thin ossified lines or fibers extend transversely across the joint. Later, bone density increases still more and the joint space cannot be detected. Calcification of anterior and posterior ligaments forming syndesmophytes is characteristic of the disease. Eventually the typical "bamboo spine" results, together with marked osteoporosis of vertebral bodies.[76, 1168] It was suggested that changes in the sacroiliac joints may be degenerative, resulting from torsional strains exerted in consequence of stiffness of the lumbar spine. [There is need for histologic studies of osseous sacroiliac lesions in rheumatoid spondylitis; until these are available one can only speculate about the nature of these changes.—Ed.]

Apophyseal joints may be involved, but apophyseal lesions are often difficult to demonstrate in roentgenograms,[1588] as are costotransverse and costovertebral joints. One writer observed the earliest roentgen changes in one or more costal or apophyseal joints,[2172] and stated that these were rarely normal in cases where sacroiliac joints were affected. Others found lesions in apophyseal joints infrequently (nine of 50 cases).[183] The symphysis pubis was fused in some instances. Roentgenographic evidences of periosteal reactions were usually a late manifestation.[2172]

Changes in the sacroiliac joints ranging from para-articular rarefaction and narrowing of joint spaces to complete bony obliteration were observed in 98 of 160 paraplegic patients.[2] The apophyseal joints and spinal ligaments were affected, the latter not so frequently as in rheumatoid spondylitis.[7]

Pathology. Muscle biopsies obtained from patients with ankylosing spondylitis did not show inflammatory changes such as have been reported in patients with rheumatoid arthritis of peripheral joints.[424, 807] One writer reported findings in a sacroiliac joint removed at necropsy from a paraplegic patient who presented roentgenographic findings "similar to those seen in ankylosing spondylitis." The joint space could not be delineated and the articular cartilages had disappeared. The subchondral bone was exceptionally vascular, the cortex thin. Microscopic examinations showed notable atrophy of bone. At one point the joint surface was denuded of cartilage and the joint appeared in the process of being obliterated.[2]

Treatment. *General.* Usual measures, including rest, physical therapy, corrective exercises and orthopedic appliances, were discussed.[561, 691, 1185, 1190, 1476, 1725, 2062] Prevention and correction of the special deformities which occur in rheumatoid spondylitis should receive attention in every case. Postural and deep breathing exercises should be stressed. When deformity has developed and the patient is stooped, efforts should be directed towards regaining lost height by stretching exercises and physical therapy.[858, 1725]

Roentgen Therapy. Roentgen therapy was repeatedly approved for treatment of rheumatoid spondylitis; nevertheless, results were difficult to evaluate. Two general types of x-ray therapy were employed: "wide field" therapy (introduced by Scott), and local therapy, especially advocated by Freyberg, and variously modified by others. Wide field therapy, though approved by some, was less popular than local therapy.[76, 77, 559, 599, 654, 807, 858, 1148, 1190, 1596, 1725, 1848, 1901, 2025, 2062, 2158] No new series was reported. At least this treatment does no harm when carefully administered. Neutropenia is an indication to stop therapy. Nausea and vomiting occur in some patients.

ACTH and Cortisone. These agents have proved as effective in this condition as in the peripheral type of rheumatoid arthritis.[175, 176, 1348, 1725] Dosage and other details of use were similar to those recommended for therapy of rheumatoid arthritis.

Chrysotherapy has been abandoned by many for treatment of rheumatoid spondylitis.[858, 1725] D-tubocurarine in an oil-wax suspension was approved for treatment of muscle spasm,[1482] but others found this measure useless.[1292] Neostigmine was carefully tested as a treatment measure for rheumatoid spondylitis and found useless.[80] An instance was reported of a patient with rheumatoid spondylitis who developed toxic symptoms after receiving neostigmine.[572]

Osteotomy of the spine was employed repeatedly, with marked improvement in some instances.[216, 865, 1184, 1185, 1594, 1982, 2053] Osteotomies of the femur and excision of the femoral heads and necks [102, 1395, 1869] and partial denervations of the hip [1492] were done for hip-joint arthritis associated with rheumatoid spondylitis.

Osteoarthritis

The division of osteoarthritis into primary and secondary, as outlined in previous Reviews, is now generally accepted. With the exception of those dealing with the hip, however, most papers were concerned with the primary type, mentioning secondary osteoarthritis only incidentally. The division between the two cannot always be sharply made. The part played by injury in producing a baseball finger at the terminal phalanx in a young man would be termed secondary osteoarthritis, and readily distinguished from the slowly developing primary Heberden's nodes of a middle-aged woman [1924]; a unilateral osteoarthritic hip developing in a young person following a slipped epiphysis is easily separated from the slowly developing spurs at the acetabular margins of elderly persons. Nevertheless, it may be extremely difficult in an obese female of 45 to determine whether the narrowing of the cartilage in the knees with osteophyte production at the margins of the joint is due to a primary degenerative condition or is secondary to the trauma incident to the continued obesity. (Several features of secondary osteoarthritis are discussed under "Diseases Related Primarily to Trauma.")

The term "osteoarthritis" is still generally preferred, while the more descriptive "degenerative joint disease, multiple" suggested by the Primer on Rheumatic Disease [326] has had extremely limited acceptance. Patients too may resent the implication of such a diagnosis.[113]

The significance of osteoarthritis in war time was shown by a study for the Mediterranean Theater, where this condition was found to account for 621 out of 2,020 hospital cases of arthritis (plus probably many of the 787 "chronic arthritis, type unspecified"), as compared to 393 cases of rheumatoid arthritis. Only 10.6 per cent of the patients with osteoarthritis returned to active duty, as compared to 21.3 per cent of the rheumatoid patients and 22.5 per cent of the "Chronic, unspecified" group.[1628]

An excellent paper on the aggravation of osteoarthritis by trauma was presented by Hanlon and Estes,[768] who suggested that compensation boards and insurance carriers are justified in recommending prolonged financial coverage of patients with osteoarthritis who have sustained injury. Of interest was the increased cost of treatment in patients having compensation or liability claims.

Clinical Aspects. Usual clinical features were again reviewed.[113, 246, 336, 560, 601, 961, 1558] "Everyone beyond middle age has some degree of osteoarthritis; only some persons are uncomfortable from it and few are disabled." [601] An interesting continuous follow-up study of 500 arthritics was compiled by Nissen.[1479] As a whole, patients with osteoarthritis lived longer than those with rheumatoid arthritis and maintained a higher level of activity. Although concerned primarily with the orthopedic aspect of the knee joint, Magnuson's paper [1279] contains valuable diagnostic aids for medical and surgical rheumatologists.

Synovial cysts over the terminal phalanges were suggested as a precursor of Heberden's nodes,[509, 1928] and were also reported to be associated with or preceded by longitudinal grooving of the fingernails.[23] Continuing their studies on the hereditary aspects of Heberden's nodes (reviewed in the Ninth Rheumatism Review), Stecher and his associates have published several statistical analyses of patients having this localized form of osteoarthritis of the terminal interphalangeal joints, comparing various factors with those in persons of similar age and sex who do not present such nodes.[1923, 1926, 1930] They noted a distinct time relation between the appearance of Heberden's nodes and the menopause in 44 of 99 women who had passed the menopause. However, they found no significant association between Heberden's nodes and hypertension or obesity. Over 85 per cent of Stecher's cases having Heberden's nodes showed no evidence of osteoarthritis elsewhere, which led him to take issue with the common belief as expressed by Monroe "that they are but part of a generalized hypertrophic arthritis, although they may be the chief sign." Nevertheless, a marked preponderance of osteoarthritis elsewhere in patients with Heberden's nodes as compared with those in a control series was apparent. Of particular interest were three original cases and nine others summarized from the literature which demonstrated that "Heberden's nodes develop only in a hand which has an intact nerve supply, which functions normally and in which the tissues are not subject to trophic disorders. The lesion fails to develop or is retarded in its progress in the presence of either peripheral nerve damage, spinal cord disease or palsies of cerebral origin." [1930] This phenomenon was explained by increased circulation due to nerve injury with resultant "demineralization of bone and protection against the development of Heberden's nodes." [These detailed studies have been conveniently summarized in one report.[1925]—Ed.] Three papers [633, 1176, 1447] discussed osteo-

arthritis of the trapeziometacarpal joint, one author [1176] describing it as the most important joint of the hand.

The cause of the pain experienced by the patient having osteoarthritis continued to be a subject of discussion.[960] It was attributed to "pressure or trauma of the extra-articular hypertrophic villous structures which develop around the borders of the osteoarthritic joint," [19a] and to the pressure of new subperiosteal osteoid tissue of the developing marginal exostoses, stretching the periosteum.[112] Hopkins [920] cautioned against attributing the pain of an osteoarthritic patient to the bony spurs visible on x-rays and thereby missing the more important "myositis" present which is usually amenable to treatment by physical measures.

Although osteoarthritis may affect any one of the peripheral or spinal articulations, any combination of these, or indeed, all of them, it is not unusual for one particular area to be affected with symptoms predominating there. Osteoarthritis of the cervical spine assumes particular importance because of the radicular symptoms in the arm which it may produce. [Papers discussing this phase of osteoarthritis are dealt with in more detail under "Brachialgia."—Ed.] Osteoarthritis of the hips and knees frequently progresses to a state requiring surgical intervention.

Pathology. An excellent review of the accepted pathologic changes in osteoarthritis was presented by Waine.[2099] The Italian anatomist Lugiato [1256] described a method for studying the changes in the fibrillar supporting framework within hyaline cartilage by the examination of unstained sections under polarized light. He demonstrated that the degenerative process began with fraying of the cartilage surface and alteration of the fibrillar system so that its regular distribution is lost. The early weakening of this system indicates loss of cartilaginous elasticity, which is then followed by erosion, marginal proliferations and, later, by invasion and replacement of cartilage by connective tissue and finally the destruction of the joint surface. [This well illustrated technic gives information not obtained by conventional microscopic examinations.—Ed.] The importance of the patella in arthritis of the knee was emphasized by Haggart,[747] who found the "two regions of the knee that generally exhibit degenerative arthritis" to be "the medial horizontal facet of the patella and along the patellar groove of the femur."

Etiology and Pathogenesis. The basic concept of pathogenesis as cartilage degeneration followed by reactive phenomena in subchondral bone was generally supported. "The influence of contributory factors augmenting the degenerative process or inhibiting its repair appears likely, but has not been fully established."[2099]

In mice fed a 29 per cent fat diet, articular aging was hastened as compared to those fed 5 per cent fat. The incidence of osteoarthritis was twice as great in those on the higher fat diet, and the onset of the disease was significantly accelerated.[1841, 1843] In another animal experiment [1168] mice were subjected to moderate daily forced exercise from the age of six weeks for a period to twelve and a half months. Litter mate controls were deprived of exercise. The controls were found to have more minor lesions in the articular cartilage than the exercised mice. There was no difference in the incidence of more severe lesions. Lanier therefore disputed the commonly accepted "wear and tear" theory of the etiology of degenerative joint disease. [This study used an inbred strain of mice, selected for high incidence of degenerative cartilage lesions.—Ed.] Ishmael [960, 961] studied "a thousand patients with secondary degenerative arthritis" and concluded that certain changes in this disease

resulted from a traumatic breakdown of joints which had been disturbed by factors known to produce the more common forms of osteoporosis and osteomalacia, and that further, when these factors were corrected, satisfactory relief of symptoms resulted. [No details are given regarding criteria for classification, or evidence that the mechanisms supposedly explaining the decreased density of bone were actually operative. Sole criterion was relief of pain following certain methods of treatment.—Ed.]

Using the thickness of certain definite points of the cranium as an index of pituitary influence on bone growth, Oldberg [1502] measured the thickness of the parietal bone by x-ray and noted an increase in a few women having Heberden's nodes as compared to women who did not have them. He therefore theorized: "The skeletal changes in the phalanges form part of a general 'subacromegalic' growth disturbance which is particularly manifest in women after the climacteric."

In papers dealing with specific etiologic factors, infection was said to play "no part whatsoever in the production of osteoarthritis."[600] Others presented an unconvincing theory linking "arthritis" (all types) to "latent phlebitis" resulting from local infection,[1380, 1381] or attempted to prove a causative rôle played by focal infection, by means of deductions from other authors' autopsy reports.[169] [We cannot agree with the conclusions drawn in either of these loosely written papers.—Ed.]

Laboratory Data. In 18 cases of osteoarthritis, there was no relationship between plasma cholesterol level, sedimentation rate and the urinary cholesterol. Urinary cholesterol excretion was within normal limits.[700] Plasma viscosity values were "in the upper range of normality and the lower part of the abnormal range."[262] It was reported that the sedimentation rate may be "slightly increased."[638]

X-ray Appearance. The accepted roentgen diagnostic aspects of osteoarthritis were outlined.[1540] The detailed x-ray appearance and evolution of Heberden's nodes were described. In addition to the well recognized joint changes, attention was called to spurs developing from the attachments of flexor and extensor tendons to the terminal phalanx, visualized only in lateral views, and to the development of irregular bony structures in the distal ends of the middle phalanges, with a foamy arrangement of trabeculae.[1928]

Medical Treatment. Fletcher [560] summarized medical treatment in osteoarthritis with the following succinct statement: "As will be seen from this description of the treatment of osteoarthritis, the situation is not very satisfactory."

Succinic acid in combination with aspirin,[2018] vitamin E orally and by inunction,[43] glucuronic acid,[895, 1559] oral undecylenic acid,[1554] para-aminobenzoic acid and salicylate,[1870] massive doses of vitamin B_{12},[1247] massage and bandaging of the lower extremities to "improve the peripheral circulation" and thereby relieve symptoms in osteoarthritic knees,[66] were all reported as being of benefit [although the evidence presented was rather unconvincing—Ed.] Calcium ortho-iodoxybenzoate [1077, 1292] and antireticular cytotoxic serum [697, 1120] were reported as ineffectual. Intravenous procaine was reported as producing "good" results in 82.7 per cent of 139 cases by one author,[703, 704] and of benefiting only one out of four by another.[1304] Procaine injections of the obturator nerve [514] and into "painful tendons" [1019] were recommended for relief of painful osteoarthritic hips. Intra-articular injections of lactic acid were recommended,[75, 191, 837, 1326] as were injections of Intracaine in oil into the "trigger points."[1201]

During the period covered in this review, observations were reported on five patients with osteoarthritis during ACTH or cortisone administration, usually given for some other disease. Relief of pain during administration, with variable degrees of recurrence after medication ceased, was recorded.[384, 854, 1157, 2057]

[We agree with Bayles[113] that "since disappearance of symptoms is the only measure of successful treatment and since they may wax and wane spontaneously, to conclude that a patient is better because of a special medication is at once most pleasant and most dangerous for the physician."—Ed.]

Physical Therapy. Accepted methods of physical therapy were outlined and their value emphasized.[214, 377, 560, 1063, 1078, 1231, 1332, 1885, 2131]

X-ray Therapy. Although Freyberg[599] stated that roentgen therapy had "failed in almost all cases of osteoarthritis," favorable reports were given by others.[625, 654, 669, 1142, 1582] [Dosages and schedules used varied widely, and often were adjusted to the patients' symptoms.—Ed.] A variant of this method of treatment was the local application of radon ointment.[1060]

Surgical Treatment. Practically all surgeons agreed that operative intervention in osteoarthritis is justified only when an adequate period of medical treatment has failed to bring relief and the patient is suffering serious disability and continued pain. "No surgical measures should be undertaken unless there is reasonable assurance that they will decrease pain or improve the function" (Kuhns). Indications for and the technic of patellectomy,[1279, 2162] and for arthrodesis of the knee,[747] were discussed, as well as debridement of the knee joint,[964, 1197] and surgical revision of arthritic feet.[1088] Excision of the trapezium[633] was recommended for osteoarthritis of the trapeziometacarpal joint, as was arthrodesis.[1447] Practically all other surgeons, however, dealt with various surgical procedures for the relief of osteoarthritis of the hip which was described as "the most disabling form of osteoarthritis."[1689] General reviews of this subject were presented.[837, 1197, 1983] The relief from pain and increased motion of the hip which may be obtained by manipulation were noted.[1140, 1197, 1689] Partial sensory denervation of the hip through section of the obturator nerve, and complete sensory denervation by the additional section of other sensory nerves to the hip, may at times be a very satisfactory procedure.[301, 1033, 1034, 1035, 1090, 1219, 1492, 2033] A detailed anatomic study of the complicated sensory nerve supply of the hip was presented.[1023] Despite its shortcomings and frequent failures, cup arthroplasty as originally introduced by Smith-Peterson in 1939 has brought gratifying relief from pain and increased motion to many severely osteoarthritic hips.[146, 785, 1181, 1182, 1865, 1964, 1965, 2192] Arthrodesis, however, has sometimes been considered the procedure of choice.[428, 932, 1167, 1475, 1535] More recently, resection angulation osteotomy has been recommended.[102, 1396, 1397, 1515]

Osteoarthritic (Hypertrophic) Spondylitis

A study of skeletal remains, including specimens from Neolithic through Byzantine periods, showed osteoarthritis to be the chief disease in each group examined. It was evident in 33 per cent of the males as compared with an estimated incidence of 21 per cent for American men engaged in heavy labor.[38] Several anatomic studies were reported.[898, 1438, 1439] In older people, nerve root compression is a frequent result of osteoarthritis. Degeneration of discs begins in the fourth decade; intervertebral spaces become narrow, and intervertebral foramina are likewise narrowed in the vertical diameter. The annulus is also pressed back, protruding into the spinal canal and reducing the size of the foramina. Overriding of apophyseal joints or misalignment is especially marked in midcervical and lumbar regions. X-rays must be taken at 45 degree angles in order to demonstrate posterior spurs encroaching on foramina.[902]

An interesting condition of the spine causing ankylosis in old people was reported. Roentgenograms showed hyperostosis most marked in the dorsal region, but

evident also from the upper sacrum to the axis in some cases. The hyperostoses were seen to arise from anterolateral aspects of vertebral bodies and extend upward in a "candle-flame" formation at lumbar spaces. In the dorsal region these appeared as thick, bony structures with a cortex and medulla lying in continuity with vertebral bodies. Osteophytes showed anatomic features different from those found in ordinary forms of osteoarthritis. The hyperostoses appeared independent of anterior vertebral ligaments. Vertebral bodies had a "woolly" appearance, more or less dense and grained. The condition is symptomless.[574]

Accessory sacroiliac articulations visualized between the ilium and posterior surface of the sacrum may show arthritic changes of varying degree which may be symptomatic. Ankylosis may occur.[745]

Backache and Sciatica

The complex character of the backache problem was reflected in a voluminous literature published during the period covered by this review. A major portion was concerned with intervertebral discs, but many other causes of backache received attention. Certain aspects of the history, physical examination and roentgenographic study which are of special interest in relation to backache were covered in the following papers[76, 238, 516, 1093]:

Backache from Lumbosacral and Sacroiliac Sprains and Strains and from Sacroiliac Subluxations. Writers on backache repeatedly stressed that changing from the quadripedal to the bipedal posture produced in man a potentially weak structure in the lumbosacral region, subject to being easily overburdened by poor posture, obesity, asthenia, and types of trauma which may result from slipping or falling. Strains resulting from such trauma may be acute or chronic. Everything possible should be done to rule out more serious lesions such as discs and tumors before a diagnosis of sprain or strain is accepted.[1004, 2063] Exact criteria for distinguishing lumbosacral from sacroiliac strains have not been agreed upon. Differentiation on clinical findings was outlined.[427] Most writers considered the mechanically weak lumbosacral region to be the most common site, in contrast to the sacroiliac joint, which is a much stronger articulation.[427, 1271, 2185]

As in previous years, some writers expressed doubts as to whether strains or sprains ever cause low back pain.[1006, 2061] "It is no longer necessary to call upon the theory of sacroiliac strain and subluxation to explain the complaints of a large proportion of patients presenting pain and tenderness in the region of the sacroiliac joints with or without sciatica. These signs and symptoms have been found repeatedly by many observers in patients presenting proven pathologic changes in the lower spinal discs and repeatedly relieved by surgical attacks on the discs" (Jones[1006]).

No radically new plans of treatment were presented. Measures considered useful included immediate rest for acute injuries, manipulations, injections of local anesthetic agents, and fitting patients with belts. Dramatic relief in cases where muscle spasm was associated with low back pain was reported to have followed injections of tubocurarine in oil.[1776]

Industrial Backache. Industrial physicians and disability commissions are confronted with many different diseases when dealing with patients who have acquired backaches during employment. In one study of 106 patients, six had fractures, neoplasms or destructive bone disease, 42 showed no visible bone injury or abnormal joint conditions, 25 showed developmental anomalies with or without bone changes, and 33 showed some type of arthritis.[2133] The numerical magnitude of the problem was reflected by the fact that during 1944, 8,546 back injuries were contested before

industrial commissions in Massachusetts. The contested injuries represented only a fraction of the total.[11]

Once a back injury has occurred in an industrial worker, proper treatment can help to minimize disability. Jobs should be assigned which permit graduated work until the employee is able to resume unlimited work. Conservative therapy should be followed wherever possible while keeping the patient at some light work, rather than allowing a complete "lay-off."[1793] Attorneys, adjusters, judges, labor leaders, patients' relatives, and patients themselves need to be informed that the best interests of all concerned are served by quickly restoring the patient to normal. The best results are obtained when care is taken to prevent or overcome intangible factors such as resentment, greed, or fear of being cheated out of deserved compensation.[2088]

Postural Backache. Attention was again called to faulty posture as a cause of low back pain.[1271, 1565] It was said to occur most often in women. The usual history was of pain localized in the lumbosacral region or extending to the buttocks and without radiation to the lower extremities. Such pain is aggravated by standing or working, and is relieved by rest. It is seldom incapacitating. Heat, massage and exercises can improve or cure many "lame backs due to poor posture." The patient should learn to flatten the lumbar spine by tilting the pelvis. He should work conscientiously at graduated exercises to improve posture.[1093, 1129, 1479, 1565] Weight reduction and a strong abdominal belt to support the weight of the abdomen are helpful for some.

Backache from Spondylolisthesis. Forward gliding of lumbar vertebrae was regarded by most writers as congenital. Some still hold that trauma may be the direct cause. The most frequent site is at the level of the fourth or fifth lumbar vertebra.[215] It was again stated, as in the Ninth Review, that spondylolisthesis may be observed in association with protruded intervertebral discs.

Spondylolisthesis cannot occur without separation of the anterior from the posterior segments of the neural arch at the affected level. This separation, designated as "spondylolysis," is not at all rare.[1383] In one study of 511 patients complaining of backache, roentgenographic evidence of this hiatus was observed in 52 instances, approximately 10 per cent. Among this group, 19 (36 per cent) showed slipping or spondylolisthesis of varying degrees.[1195] Spondylolysis or spondylolisthesis was found in 8.5 per cent of 811 cases of backache, an incidence thought to be somewhat low because some roentgenographic examinations were incomplete.[617] Spondylolysis may be demonstrated by oblique roentgenogram when usual anteroposterior and lateral views fail to disclose it.[16] In a 24 year old soldier with low back pain, roentgenograms showed progressive development of a translucent area or separation at the pars interarticularis; a cleft appeared and in a few weeks became complete. This resembled stress fractures such as "march fractures" of metatarsal bones.[1686] One writer believed that surgery is invariably necessary to effect relief for spondylolisthesis in older persons.[1093]

Backache from Reverse Spondylolisthesis. Posterior displacement of the fifth lumbar on the first sacral segment, and of other vertebrae at various levels, is not a separate entity, but a mechanical consequence of degenerative disc disease. Roentgenographic studies of 600 individuals, made during the course of examinations for backache, disclosed posterior displacement of the fifth lumbar on the first sacral segment in 56 instances. This condition was attributed to narrowing of discs, allowing backward and downward displacement of overlying vertebral bodies. Among patients who showed this defect, severe low backache and sciatica were more frequent than among patients without this condition. Surgical removal of herniated discs without spinal fusion gave poor results.[562] Backward displacement of vertebral bodies cannot be detected in some instances unless roentgenograms are taken while the patient is

standing. The effect of displacement may be only a fraction of an inch, but this bespeaks unstable apophyseal joints. Individuals with this condition were said to have potentially weak backs, and to be subject to repeated episodes of pain. Some have sciatica as well as backache. Eventually, arthritis may appear in apophyseal joints.[562, 1091, 1271, 1860]

Backache and Sciatica from Primary Sciatic Neuritis. Although an inflamed sciatic nerve has rarely been seen or examined, three cases were reported showing gross swelling of the affected root, without discoverable mechanical cause. In two additional patients the root was normal in size but there were adhesions between it and surrounding structures.[914] [These instances suggest that primary sciatic neuritis may indeed be a significant problem and not merely a "wastebasket" diagnosis for instances in which the true cause cannot be discovered.—Ed.] True sciatic neuritis, or interstitial neuritis, was again attributed to diabetes, to alcohol and arsenical poisoning, to local or general "fibrositis."[901] Some believed that primary radiculitis of the sciatic nerve roots could be differentiated from the disc syndrome on the basis of differences in spinal fluid findings, response to rest and clinical observation.[20] Others observed that the signs and symptoms of herniated discs were indistinguishable from those of sciatic neuritis, and found that the latter diagnosis had been virtually supplanted by that of herniation of a lumbar intervertebral disc.[466]

Backache with Osteoporosis. Radiography was considered the only satisfactory means of detecting this condition. Only 10 of 32 patients with generalized osteoporosis complained of pain or discomfort, and of 181 patients aged 40 years or more who complained of back pain, 30.9 per cent showed osteoporosis. Blood calcium, phosphorus and alkaline phosphatase levels were the same in persons with osteoporosis as in those without. A roentgenographic survey of spines in 227 patients indicated an increasing incidence of osteoporosis with advancing age. This was observed in both sexes, but the frequency was higher in women who had had repeated pregnancies. Balance studies showed that elderly patients with and without osteoporosis are able to absorb and retain calcium and phosphorus from food. Lack of exercise was thought to play a minor rôle in the senile type of osteoporosis.[1079]

An important contribution to the subject of osteoporosis was made by Reifenstein and Albright,[1660] who found that osteoporosis is not a disease of calcium or phosphorus metabolism; rather, it is a deficiency in the protoplasm of bone matrix laid down by the osteoblasts. Of eight etiologic subgroups, postmenopausal osteoporosis was the most common. Metabolic studies demonstrated that estrogens and androgens can bring about a decreased excretion of nitrogen, calcium and phosphorus; the effect on calcium metabolism of administering estrogen and androgen in combination was greater than that from administering either alone. Results of treatment with estrogens alone and in combination with testosterone were considered satisfactory in "a large number of cases." Within a period of weeks or months, pain in the spine and other bones was noticeably improved. It has been difficult, however, to produce undisputed evidence that this treatment brings about better calcification of bones. Anderson[36] confirmed the clinical and metabolic effectiveness of Dienestrol, and recommended a high level of intake of calcium and phosphorus and moderate doses of vitamin D (10,000 I. U. daily), as well as estrogens. It is necessary to rule out hyperthyroidism, hyperparathyroidism, multiple myeloma and metastatic malignancy,[36] and to make carefully individualized programs of treatment for patients with this condition.[860]

Backache from Hypertrophied Ligamentum Flavum. Although some writers do not consider that hypertrophy of the ligamentum flavum can be a cause of root pain, this lesion was definitely identified in three patients. In two, hypertrophy was said to have followed trauma caused by a lumbar-puncture needle. Backache with

sciatic pain had caused almost complete disability. Thickening of the ligamentum flavum was observed at operation. After the operation, pain subsided slowly.[914, 1647]

Backache from Metastatic Lesions. Carefully taken histories may yield important clues leading to a correct diagnosis of metastatic disease in some patients with backache. Symptoms of this condition may be misleading, however, and may simulate a protruded disc. Muscle spasms are not uncommon, and pressure on the posterior spine of involved vertebrae may be extremely painful.[539]

Backache from Urologic Lesions. Urologic lesions identified as causes of backache included kidney infections, tumors, chronic prostatitis and seminal vesiculitis.[2047]

Backache from Gynecologic Lesions. "Abnormalities of the female pelvis can and do cause backache but probably not as frequently as they are supposed to." Lesions of the cervix, pelvic inflammatory disease, ectopic pregnancy, uterine fibroid tumors and large ovarian tumors were said to be occasional causes of backache.[2063] Postoperative backache was attributed in some cases to tension or pull on approximated broad ligaments following pelvic operations. Severe retroversion was said to cause backache in some women.[2047]

Backache from Gastrointestinal Lesions. Back pain referred from the viscera is easy to explain when the diseased organ impinges upon the posterior peritoneal wall or upon the back structures behind the peritoneum, as in retroperitoneal tumors, pancreatic tumors and duodenal ulcers. When the diseased organ is at a distance from the posterior peritoneal surface, the mechanism of backache is not always clear. In some instances, inflammatory irritation of somatic nerve fibers in the mesentery explains the pain; in others, it is necessary to call upon the concept of a viscerosensory reflex for an explanation. When backache occurs in regional ileitis, reference of pain to the back may result from involvement of somatic nerve fibers in the mesentery. Hiatus hernia and aerophagia cause backache in the upper dorsal and lower cervical region. In such instances, pain is presumably referred along pathways identical with the sensory pathways for pain arising in the heart.[2074]

Unlike back pain resulting from diseases of the spine, that caused by intra-abdominal disease is not accompanied by muscle spasm, limitation of motion or changes in the spinal curvatures. It is often aggravated by lying on the back, although the patient is able to engage in active physical exercise during the day. At times it is relieved by assuming positions in which the spine is flexed.[2074]

The Dorsolumbar Syndrome. The dorsolumbar or thoracolumbar syndrome was said by one writer to be responsible for 10 to 15 per cent of the cases of low back pain.[972] The articulation between the twelfth thoracic and first lumbar vertebrae is subjected to marked strain, since it is the first movable joint below the relatively fixed thoracic column. Neither disc diseases nor actual compressions of nerve roots have been shown to cause this type of pain. Since the twelfth rib articulates with the vertebral body by a single facet, motion is possible in all planes. When other ribs are elevated, the twelfth rib may be depressed by the action of the diaphragm, with resulting pressure on the twelfth thoracic nerve lying just below. This syndrome causes burning pain often designated as "causalgia" or "neuralgia." Scoliosis is frequently present. Skin hyperalgesia in an area corresponding to the involved dermatone may be noted. A most important step in treatment is correction of postural defects. Applications of heat, massage and use of a corset are usually helpful. Paravertebral nerve block was said to give remarkable relief during the acute phase.[972] [In the investigation of low back pain, it is important that x-ray studies include the dorsolumbar area.—Ed.]

Backache from Osteochondritis or Adolescent Kyphosis (Juvenile Epiphysitis; Scheuermann's Disease). An outstanding feature of this condition is the exaggeration of the dorsal curvature, usually in rapidly growing girls, less often in boys.

The age at onset for girls is between 12 and 13, and for boys between 15 and 16 years. Treatment is sought usually because the child complains of stiffness and shows increasing stoop in the dorsal region. [It is often asymptomatic.—Ed.] Roentgenograms at first show added density of epiphyses, later epiphyseal fragmentation. In severe cases fragments of epiphyses may be displaced and a translucent area appear between the epiphysis and the body. Ultimately, a destructive process may involve a considerable portion of the vertebral body and the intervertebral space may be diminished. Under these circumstances the bodies may become so closely approximated that secondary hypertrophic changes develop. Ossification of epiphyses proceeds in an irregular manner. Curvatures exaggerated by this process eventually become fixed.[205] The cause is unknown. Kemp and Wilson[1060] reported that several members of two families were affected by spinal osteochondritis. Postural deformities and malnutrition during the years of growth were thought to be influential in causing this condition. It was noted that postural deformities appeared before osteochondritis was evident in roentgenograms. There was concomitant evidence of dental fluorosis in several patients.[1059, 1060]

This condition must be differentiated from tuberculosis and compression fracture.[2153] Treatment should include orthopedic appliances to keep the spine in a position of normal extension, in order to prevent increasing kyphosis, limit the extent of nuclear herniations and maintain normal distribution of forces throughout the vertebral column. [Associated minimal vertebral lipping in adolescent kyphosis should not be confused with osteoarthritis.—Ed.]

Backache from Spasm of the Levator Ani, Coccygeus and Pyriformis Muscles. Pain from spasm of the levator ani muscles was said to be felt at the lower border of the sacroiliac joint, about the sciatic notch, at times in the hip or along the course of the sciatic nerve. Frequently, there is a history of falling on the buttocks in a sitting position. When the levator ani muscle is at fault, rectal examination may disclose tenderness on pressure over affected muscles. A spastic pyriformis is recognizable during rectal examination as a "sausage-shaped" mass. Pain is attributed to pressure of the swollen spastic muscles on the sciatic trunk. Recommended treatments included manipulation of the coccyx through the rectum, massage of the spastic muscles and section of the pyriformis muscle.[1693, 1769] (The latter was said to bring about immediate and permanent relief.)

Backache from Diseased Articular Facets. The term "facet syndrome" was suggested by Ghormley to designate instability of one of the small posterior articulations in the spine. It occurred mainly in the lumbar region and was said to result from traumatic subluxation or dislocation. Characteristically, the patient felt a snapping sensation in the back while straining, had immediate pain, and listed to one side in some degree of flexion. Pain might radiate to the groin or along the sciatic nerve. If the underlying lesion was subluxation, posture returned to normal with rest. If dislocation occurred, additional measures, even surgical fusion of the spine, were needed. Roentgenograms at times were negative at first, but in time showed narrowing and even hypertrophic changes in the affected apophyseal joints. The adjacent nerve root could be compressed by mechanical narrowing of the foramen and edema in soft tissues. It was said that many cases once thought to be "facet syndrome" are in reality disc lesions. If doubt should exist concerning the diagnosis, exploration of the disc was recommended, accompanied if necessary by foramenotomy.[2185]

In addition to traumatic lesions, apophyseal joints may also suffer other forms of articular disease. Narrowing of intervertebral discs with accompanying loss of stability may result in stretching of ligaments, abnormal wear and tear on apophyseal joints. Progressive sclerosis and hypertrophic changes develop. Patients with these conditions may experience localized pain due to the arthritic process, radiating pain

due to compression of nerve roots, and diffuse pain due to muscle spasm. Spinal fusions with prop type and H type grafts were recommended. Many of these patients can be treated satisfactorily by conservative measures.[516, 903, 1752, 2157]

Backache from Congenital Anomalies. Usual congenital deformities were reviewed. No new data were added.[1275, 1406, 2185]

Psychogenic Backache. The general aspects of psychogenic rheumatism are considered in a later section, but psychogenic backache enters into the differential diagnosis of all patients with backache. This diagnosis should not be made by exclusion but should be based upon recognizable features which can be detected during the course of careful history-taking and physical examination. Psychogenic backache is to be distinguished from malingering.[1416, 1539, 1793]

When a question of compensation was involved, the picture was quite distinctive. There was always a definite history of trauma which the patient could give in tedious and ramifying detail. Onset of pain was said to be immediate. Work was 100 per cent painful. There was no postural help for these people; they were just as miserable lying down as sitting up or standing. They were unable to sleep at night even with analgesics and sedatives. Bending exaggerated their symptoms. They knew of no mechanical measures to improve their discomforts. Radiation of pain was unpredictable, except that it was not along established physiologic courses. There were frequently additional complaints. During examination, the patient often maintained a bizarre posture. Extensive areas of tenderness were noted at times. Sensory examinations often yielded hysterical patterns of anesthesia.[539]

Among patients in military service who were suffering from nervousness, insomnia, tension and irritability, backache was frequently an associated complaint. In some instances definite organic diseases were found, but other patients were simply suffering from hysterical conversion symptoms.[1539] In military service, an individual with psychogenic backache directed attention away from defects involving his personality, "attempting to focus attention upon his back instead of upon himself."[1416]

Physicians not sensitized to these subtleties of musculoskeletal neuroses frequently miss the diagnosis of psychogenic back disorders. Often such patients are erroneously treated with back braces, manipulations, operations, or with prolonged physical therapy. These treatments do not relieve the pain and may increase invalidism by causing fixation of symptoms.[1539]

Backache and Sciatica from Osteitis Condensans Ilii. This term refers to a disturbance of the normal architecture of the ilium adjacent to the sacroiliac joint. X-rays show increased density, occasionally extending to the joint but not involving the sacrum; changes may involve one or both joints, be limited to the lower portions, or extend throughout their entire length. All of the patients in one series were white women between the ages of 19 and 44 years. The onset was often noted during pregnancy or after delivery. Subsequent pregnancies tended to exaggerate the symptoms. Backache was the chief complaint. Pain sometimes radiated into one or both buttocks but was not generally referred along the sciatic nerve. Symptoms were aggravated by activity and relieved by rest. Physical findings were often limited to an increase in lumbar lordosis, with spasm of spinal muscles in severe cases. Tests for sacroiliac disease generally proved negative. The diagnosis was most often confused with rheumatoid spondylitis.[1826]

Histologic examination showed bony trabeculations greatly increased in density, scattered islands of cartilage at a considerable distance from the joint surface, focal areas of fibrosis in the bone marrow, and evidence of increased osteoblastic activity. These findings were thought to represent a low-grade nonspecific ischemic process.[1826] Juvenile epiphysitis was observed in each of six patients in whom spine films were taken, suggesting a common etiologic factor.[2080]

With conservative treatment (postural training, weight reduction, rest periods,

bed-boards and, in some instances, an adequate corset), 30 of 100 patients were completely relieved, 38 reported major though incomplete relief, 23 were moderately improved and eight showed little or no improvement. In six patients, evidence of sclerosis in roentgenograms was appreciably less following these treatments.[1826]

Backache Due to Herniation of Fascial Fat or Episacroiliac Lipomas. These are discussed under Disorders of Fatty Tissues, as a form of Nonarticular Rheumatism.

Backache and Sciatica from Diseased Intervertebral Discs

This subject continues to interest rheumatologists, as well as orthopedists, neurosurgeons, industrial physicians and many others. Many papers were devoted to this problem; not all can be reviewed in detail. However, outstanding works published during the period under review and trends of developing knowledge in this field are indicated.

Historical Features. Excellent reviews described historical and outstanding clinical features of intervertebral disc syndrome.[96, 736, 863, 966, 1006, 1083, 1210, 1400, 1501, 1564, 1912] Fifteen years ago no specific therapy was available for patients suffering from "chronic sciatica" or "chronic sciatic neuritis." Rest, traction, back supports, physical therapy and manipulations were prescribed, and various injections were made in the region about the sciatic nerve. Despite these measures, many continued to suffer and some were forced to resign themselves to chronic pain and invalidism. Even as late as 1929 the intervertebral discs were considered relatively invulnerable. Evolution of present concepts of this disease has greatly changed this picture. Knowledge is incomplete but increasing rapidly. Acrimonious debate and empirical speculation are giving way to agreement on the basis of documented and verified information.[96]

Anatomy and Pathology. When intervertebral discs removed at operation were compared with discs in cadavers, degenerative changes in the two groups were similar, though perhaps more marked among discs removed surgically. There was no evidence to support the view that edema is an important factor in producing pain.[475] Some discs with intermediate stages of degeneration showed fibrous bundles of the annulus cut off at the periphery, as though surface portions of disc tissue were digested and absorbed. Microscopic studies disclosed granulation tissue adjacent to necrotic and degenerated portions of discs (presumably an effort to absorb necrotic tissue rather than to repair it). Such absorption presumably accounted for disappearance of prolapsed tissue and clearing of symptoms in some cases.[1222]

The nucleus pulposus is soft and pliable but moderately tough. It serves to distribute pressure evenly over the cartilaginous surfaces of vertebral bodies, acting as a cushion. The stronger anterior longitudinal ligament seldom ruptures.[202] Rather, ruptures occur through the posterior portion of the disc capsule, where greatest traumatic forces are exerted. Laterally, the posterior longitudinal ligaments are thinner, hence rupture is most likely to occur here near the exit point of nerve roots.[1262] Some favored the view that the nucleus pulposus is expansile[275]; others considered it incompressible and nonexpansile but plastic, obeying the laws of fluids.[958, 1912] It was recognized that tension exerted by the annulus maintains the nucleus under pressure even when weight is not being borne. If the nucleus escapes, the disc acts like a washer resisting direct force, and motions cause pressure upon the relatively small surface area of the lamina so that it is eventually ground between adjacent vertebral bodies.[1912] Resiliency and motion of the spine are not due to any elastic turgor of the nucleus, but to elasticity of ligamentous structures. The most important of these

is the annulus, composed mainly of fibrous and elastic lamellae. Extrusion of nuclear material through this tissue occurs because of the internal wearing of fibers, followed by their partial or complete rupture. Escape of nuclear tissue results in loss of internal pressure, collapse and narrowing of intervertebral joint spaces, osteophyte formation at vertebral margins, and subluxations of zygapophyseal joints in which degenerative changes develop.[958]

A study of 99 cadavers showed protruding intervertebral discs in 63 per cent. Cervical discs were protruded twice as often as lumbar discs, which were in turn four times as numerous as thoracic protrusions. In nearly half the cases protrusions were multiple. Ruptures of the annulus were not observed in 32 per cent of those showing protrusion, but the annulus was stretched and bulged posteriorly.[752] Anatomic and pathologic investigation indicated that the mechanism of intervertebral disc protrusion is not uniform. These conditions were found: (*a*) bulging discs without a rent in the annulus and without detachment of the disc from bone; (*b*) herniated discs, with traumatized lamellae and protrusion of material through a rent in the annulus, and (*c*) "slipped disc," where loss of attachment to the cartilaginous epiphyseal plate permitted posterior dislocation of the disc.[1208] [These different types of lesions may account for variation in results of diagnostic procedures and in results of treatment. The distinction is accepted as important by most orthopedic surgeons, but is not considered important by many neurosurgeons. Some authors use the term "protrusion" to indicate all types of disc lesions; others restrict it to group (*a*) above, as synonymous with bulging. In this review, protrusion is used in a general sense but, where possible, distinction is made between herniated discs and bulging without rupture.—Ed.]

Factors in Pathogenesis. Discs may protrude because of pressure exerted during positive acceleration experienced by pilots. In two cases typical symptoms and findings followed a particularly sharp or rapid "pull-out" from a dive; in one, the diagnosis was proved at operation.[1816] Roentgenographic studies of the spine made during experiments with the human centrifuge showed no significant narrowing of intervertebral spaces while force amounting to 6 G was being applied.[324] One third of 169 patients with protruded discs had sustained fractures of the epiphyseal plates, which freed the discs from their anchorage and permitted eccentric posterior portions of the disc circumference to slip backward. Sharp edges of fractured bone damaged the annulus in some instances. No evidence of primary disease in the disc was found, and trauma seemed the sole cause in these cases.[1208]

Ruptures or protrusions of discs also occur as acute episodes in the progressive, aging process brought about by natural causes.[1288] Discs mature and age more rapidly than other tissues. Their resiliency and flexibility, dependent on water content, are considerably decreased by the twenty-fifth year. At age 35 the disc is made up almost entirely of fibrous tissue. These factors may explain why discs rarely rupture in young persons and why ruptures are common in middle-aged persons.[1639] A familial factor was suggested by the observation of six of seven members in one family with "sciatica" that was relieved by surgical removal of herniated discs; none gave a history of direct or indirect trauma.[1289]

Additional instances of lesions of intervertebral discs caused by lumbar puncture were reported.[73, 978, 2179] Experiments on dogs indicated that weakening of the posterior portion of the annulus was primarily responsible for protrusion of intervertebral discs; changes in the nucleus were of secondary importance.[1087, 1089]

Cervical Discs. Cervical discs are much less commonly affected than those in the lumbar region. Otherwise, these syndromes have much in common. Discs at the lower end of each segment were most often affected, and the history is one of spinal discomfort associated with referred root pain.

One mechanism of injury described by patients with prolapsed cervical discs

took the form of sudden alteration of position following a push or sudden shift of a load when muscles of the neck were not on guard.[20] In one series trauma was the precipitating factor in one-half of the cases.[1562] Patients sought advice because of the pain in the lower cervical region or shoulder radiating to the arm. Most of the patients were past 40 years of age.[977] Headache was a fairly common symptom.[1627]

Stookey originally described three neurologic syndromes resulting from rupture of the cervical intervertebral discs: bilateral cord compression from bilateral medial protrusion, unilateral cord compression from unilateral medial protrusion, and nerve root pressure alone without spinal cord involvement, from lateral protrusion. For some time, most cases recorded were those with compression syndromes, but more recently recorded cases have been predominantly those of the lateral protrusion type with nerve root pressure. Descriptive papers outlining findings in these various types of cervical disc lesions were numerous.[20, 206, 247, 826, 977, 1133, 1392, 1810, 2240] Median protrusions may simulate multiple sclerosis and other degenerative disease of the spinal cord. They rarely give rise to pain, stiffness or tenderness, and roentgenograms may show changes so slight as to be of no diagnostic aid. Outstanding in instances of central herniation are muscular spasticity of the lower extremities and disturbances of equilibrium. Pain sensibility may be reduced, but sphincter control is usually not affected. Obstruction of spinal fluid circulation is rare, but total protein content of spinal fluid may be moderately increased.[247, 1133] Lateral protrusions cause severe pain in the neck and sometimes over the precordium, the rhomboid area or in the arm. Pressure upon the head and inclination of the head toward the affected side often reproduce the pain. Symptoms are aggravated by coughing, sneezing or straining.[826]

Although the diagnosis may be made solely on the basis of clinical findings, roentgenograms may provide helpful confirmatory information.[247, 1450, 2163] Conservative treatment of cervical discs, including head traction and physical therapy, frequently results in relief of symptoms. However, if pain persists operation should be undertaken.

Thoracic Discs. Protrusion of intervertebral discs in the thoracic region seemed rare to one writer [20] but was observed rather frequently by another.[2240] The eleventh thoracic disc was most frequently affected. Protruding discs in the lower thoracic segments sometimes caused pain which radiated to the abdomen, mimicking disease of abdominal viscera, especially the kidney. Conservative treatment of protruded thoracic discs was often successful because the thoracic spine splints itself, thus aiding recovery.[2240]

Lumbar Region. A large number of papers dealt with this subject; many took the form of reviews.[96, 275, 1086, 1210, 1578] The problem of protruded lumbar discs was frequently encountered during World War II among American military personnel. Military surgeons were disappointed in results of treatment of ruptured disc by any method, and a majority of soldiers whose cases were so diagnosed ultimately were given a medical discharge.[2221] Midline bulgings of lumbar intervertebral discs were considered causes of low back pain which a patient may experience prior to onset of sciatica.[1087, 1262] Although much less common than in adults, instances of bulging lumbar discs were recorded in older children and in adolescents.[1085] In some instances bulging discs "pop in and out." Young cited such an experience during an operation.[516]

Diagnosis. Symptoms, physical findings and results of special diagnostic procedures for detecting protruded lumbar discs were reviewed in many papers.[20, 863, 1061, 1564, 1647, 2239] Back pain often preceded the sciatic pain, which was regularly increased by coughing, sneezing or straining. Localized paresthesia and muscular weakness were often mentioned. Notable findings on physical ex-

aminations were limited forward bending, sciatic pain from paravertebral pressure, reduced lumbar lordosis, sciatic scoliosis, aggravation of pain with stretching of the sciatic nerve, also disturbance of the gait or carriage. Diminished ankle and knee jerks, sensory loss and local motor weakness were frequently found. Special clinical findings considered helpful by some were "interlaminal tenderness" [55] and the "crossed or well-leg-raising test." [2217] Contralateral pain was observed repeatedly in patients with protruded disc, indicating the need for thorough exploration at the time of operation.[1031, 2281]

Other conditions to be considered regularly in differential diagnosis included tumors of the cauda equina, congenitally defective fifth lumbar vertebrae with destruction of articular processes, spondylolisthesis, psychological problems, primary radiculitis, tuberculosis of a lumbar disc,[20] chronic arthritis (both rheumatoid and hypertrophic), and low back strains.[1210, 2289]

Myelography. Contrast myelography was widely approved as a means of diagnostic study, but there was no unanimity as to indications for this procedure. Air, oxygen, Thorotrast and Pantopaque were again discussed as contrast media.[571] Myelographic examination, like other laboratory procedures, can be misleading if the clinical investigation is neglected. Defects noted during myelography were more likely to be in error than were definite neurologic findings.[202]

Some employed myelography almost routinely in patients suspected of having a disc protrusion.[96, 702, 914, 1238, 1616, 1792, 2064, 2221] Others reserved this procedure for patients in whom the diagnosis was in doubt, where multiple or bilateral protrusions or a tumor was suspected, or where the level of the lesion was in question.[202, 473, 572, 736, 1083, 1139, 1262, 1493, 1501, 1564] Key preferred to use myelograms only in cases where he planned to operate.[1086] One writer condemned the procedure as useless and dangerous.[2241] Several variations in technic for myelography were recommended.[98, 571, 1083]

Opinions varied as to what symptoms might be attributed to allowing oily substances used for contrast myelography to remain in the spinal canal. Some patients complaining of pain along the course of nerves or of low-grade headaches were found to have Pantopaque along the nerve sheaths and in the basilar cisterns.[1302] In approximately one fourth of patients, roentgenograms taken at intervals after myelography with Pantopaque showed small amounts of this substance in the basal cisterns.[1543] In some patients this was associated with mild meningeal irritation.[1638] Upon completion of myelographic examinations, Pantopaque should be removed by gentle aspiration.[202]

Accuracy of myelographic diagnosis was discussed.[571, 702, 736, 1564, 1792] It was generally agreed that clinical evidence was more important than the myelogram. The latter frequently failed to reveal laterally placed lumbosacral "discs." False-negative myelograms were much more frequent than false-positive myelograms. When myelography is used as the sole diagnostic criterion, errors will occur in 25 to 35 per cent of the cases when both positive and negative myelograms are calculated, rather than in 6 to 8 per cent when only positive myelograms are considered.[1792] In a series of 253 myelograms, the greatest source of error was in the group of 27 patients with negative myelograms and positive findings at operation.[571] In 196 cases treated by operation, myelography was misleading in 25 to 30 per cent; errors took the form of both falsely positive and falsely negative myelograms.[736] One writer was greatly impressed with the importance of ordinary roentgenograms; useful findings included narrowing of intervertebral spaces with localized osteoarthritic changes.[18, 643] **[These changes may not appear until months or years after onset of protrusion. Meantime the patient may suffer serious, even irreparable damage.—Ed.]**

Treatment of Protruded Discs. Principles to govern choice of therapeutic procedures were reviewed in many papers. In general, the opinions expressed were similar to those noted in the previous Rheumatism Review. Recognition that protruded discs may account for troublesome instances of low back pain and sciatica constitutes a definite advance in medicine. However, the enthusiasm with which this discovery has been accepted (as an indication for surgery) has often exceeded the bounds of common sense.[18] There should be a clinical test of conservative treatment, and no patient should be subjected to operation until he has been given a period of bed-rest. Leg traction, manipulation and hot packs may also prove beneficial. Surgery is justified only when symptoms persist or recur in spite of adequate conservative treatment, properly supervised and controlled.[18] Recovery from painful and disabling experiences following protrusion and rupture of discs has occurred in many individuals during "thousands of years before the medical profession became aware of this new clinical entity."[2064] As many as 90 per cent of patients are relieved by conservative measures alone.[10]

Immediate operation was recommended for patients with large protrusions involving the cauda equina and associated with severe neurologic disturbances.[1449, 1493] Surgery should also be carried out if severe pain persists for several weeks in spite of conservative measures, and should be performed during attacks and not during remissions.[272] Absence of Achilles or patellar reflexes is not sufficient reason to undertake operation, as these are not more likely to return after surgical than after conservative treatment.[10, 702]

After acute symptoms subside the lumbar spine should be protected with either plaster jacks, rigid braces or well-fitted corsets.[467] Recurring episodes were avoided by preventing strains of the lumbar spine, but in some patients attacks recurred in spite of caution, apparently precipitated by the usual activities of ordinary living.[1449] Manipulation may be followed by spectacular recovery in some instances, but this seldom brings permanent improvement and may be harmful.[1501]

In general, operative results were best when orthopedic surgeons and neurologic surgeons worked together as a team,[1449] when operations were performed on younger individuals with definitely herniated discs, and when extruded material was completely removed. After many attacks, when thinning of the disc had resulted in overriding of apophyseal joints, and in secondary arthritic changes, pain was apt to continue unless spinal fusion was also performed.[870, 786, 1210, 1578, 2064] Narrowed foramen with mechanical infringement on the nerve roots often follows narrowing of the interspace. Exploration of the foramen with facetectomy was recommended when no pathologic condition was found to explain the symptoms.[473, 1752] Some poor results following surgery were attributed to intrathecal inflammatory thickenings,[516] to incomplete exploration, or to the overlooking of protruding tissue on the opposite side.[2231]

Many papers reported statistics on results of surgical treatments in patients with ruptured discs. Results were satisfactory in 58 per cent of the cases in one series,[18] in 77 per cent in another,[1130] and in as many as 90 per cent in others.[786, 1238, 1262, 1495, 1616]

Sciatica

General Comment

Sciatica may be caused by interstitial neuritis, but more often is the result of pressure on nerve roots by protruded discs or tumors. The diagnosis of "sciatica" has been almost supplanted by that of herniation of a fourth or fifth lumbar intervertebral disc.[1885, 1578] Nerve roots and nerve trunks may be involved at

various levels and the processes are accordingly labeled as radiculitis, ganglionitis, funiculitis, plexitis or neuritis.[1578] Prolapsed intervertebral discs, tumors, synovial proliferation incidental to apophyseal joint arthritis, varicosities of outgoing roots, spinal arachnoiditis and neuromata of nerve roots can produce the symptoms.[516, 736, 1275, 2157] Several unusual causes of sciatica were observed. These included pressure from a hydatid cyst in the body of the sacrum,[525] neuroma of the sciatic nerve, contrast media in sheaths of the sciatic nerve roots following myelography,[619] perineural cyst of a sacral root,[2031] and neurofibroma of the cauda equina.[1030]

The term "arthrogenic sciatica" was used to designate sciatic pain resulting from involvement of the funicular segment roots lying close to arthritic apophyseal joints. Swelling and redness of a nerve root in absence of prolapsed nuclear material were observed at operation. In one patient, the articular cartilages of an excised apophyseal joint showed changes attributed to degeneration in corresponding intervertebral discs, resulting in strain on the apophyseal joints, capsular ligaments and periarticular structures. This condition closely simulates the "disc syndrome." Roentgenograms generally show sclerosis and irregularity of joint margins or narrowing of joint spaces.[2157]

Gout and Gouty Arthritis

The literature reflected an increasing interest in both the clinical and investigative aspects of gout. Several excellent general reviews appeared,[140, 740, 885, 2019] and also descriptions of the classic clinical features and methods of treatment.[99, 601, 746, 1169, 1223, 1339, 1458, 1748, 2020, 2021, 2023] There were important advances in understanding of the hereditary aspects of the disease, and the use of the isotope tracer technic gave promise of revealing some of the mysteries of purine and uric acid metabolism. Results of studies based on advances in endocrine physiology carried possible implications for the pathogenesis and treatment of gout.

Incidence. In patients with arthritis, gout accounted for 3 per cent of two groups,[616, 1893] 1.5 per cent of another,[666] and 16 per cent of a fourth.[1478] [We cannot accept the rather loose criteria for diagnosis in this last series.—Ed.] Gout was diagnosed in 0.8 per cent of 4,500 consecutive industrial accident cases, and in the same percentage of 6,000 private patients.[1103] Many racial stocks were represented in a series of 100 patients reported from Boston; nine women were in this series.[1339] Another report described three Negro brothers with gout.[226]

Clinical Data. Jones[1002] described vividly and minutely the subjective and objective characteristics of acute podagra. Emphasizing the periarticular location of the involvement, the unique qualitative characteristics of the pain, and the association of localized vascular phenomena and suppression of sweating, he reviewed evidence suggesting that the acute attack of "classical or regular gout is in fact a syndrome connected with some disturbance of the vasomotor nerves controlling the periarticular plexuses." Extensive arteriovenous anastomoses around the great toe were demonstrated. [This is an important contribution to a better understanding of the local pathologic physiology of acute gout. We agree with the author that "to postulate that the seat of the disease is *in* the articulation is a mere supposition."—Ed.]

The great toe was the site of the first attack in 78 per cent of cases in one series, and was involved eventually in 97 per cent. Other sites of primary attacks were the

ankle in 21 per cent, the foot in 18 per cent and the knee in 9 per cent; cervical spine, hips or sternoclavicular joints were not involved in the first attack. Subcutaneous tophi were found in the ears of 32 per cent.[1339] The acute attacks may be polyarticular rather than restricted to one joint.

Bernstein emphasized the occurrence of gout in early life; in seven reported series, initial attacks occurred before the age of 21 years in 2.5 per cent of cases, and before the age of 31 in 21.7 per cent. Six cases with onset of gout between the ages of 12 and 16 were well documented[140, 826]; the disease was severe and progressed rapidly in these young patients. In another series, the initial attack occurred in 14 per cent before the age of 30; the average age at onset was 46.8 years.[1339]

Of 100 patients with gout, 14 were accustomed to eating large amounts of meat; 26 used alcohol frequently and 28 moderately. "Obesity of a degree to warrant comment was recorded in 41."[1339] In an industrial group of 38 patients, seven used alcohol freely and two were abstainers, while in a comparable group of private patients, there were 23 who admitted daily use of alcohol, and seven were total abstainers.[1108] A lower standard of living was not necessarily a protection against gouty arthritis.[2020] No association was noted with lead poisoning.[855, 2020]

Association of gout with hematopoietic disturbances was reported.[140, 1075, 1834, 1902] One instance of association of gout with rheumatoid arthritis was reported.[2021] This 50 year old man provided all accepted criteria for the two diseases except for demonstration of subcutaneous tophi. "Osseous tophi" were demonstrated by x-ray and a typical rheumatoid nodule by biopsy. Two fatal cases of fulminating gout with extensive urate deposition were reported.[1075, 1902]

Provocations of Acute Attacks. Drinking bouts, unusual physical activity, vigorous religious fasting or too rapid weight reduction seemed to precipitate acute attacks.[1458] "The most common cause of acute arthritis following a surgical operation in a man is gout."[1458] Harkavy[782] reviewed the rôle of allergy in gout and reported three patients in whom acute gout attacks were induced by deliberate subcutaneous injections of pollen extracts or by the synergistic action of allergenic foods and pollens.

Conditions which seemed to provoke attacks of gout in 44 of 100 patients were: moderate to excessive walking in nine, mild trauma to the foot or toes in eight, alcoholic indulgence in seven, respiratory infections in five, "holiday season" in four, parenteral liver extract in three, minor surgery in three, and diathermy treatment, cardiac failure, acute cholecystitis, Sippy diet and bleeding duodenal ulcer each in one patient.[1339]

Administration of ACTH to gouty patients during a symptom-free interval may be followed by acute gouty arthritis.[841] Other studies indicated that such attacks may be related to abrupt withdrawal of ACTH.[740, 841, 1702, 2204] It has been suggested that stimulation of adrenocortical function is a common pathway through which various precipitating factors can operate to produce acute attacks, and that the use of ACTH, or its sudden withdrawal, may serve as a provocative test for this disease.

Etiology and Pathogenesis. *The Factor of Heredity.* The inconsistent hereditary pattern of clinical gout and the observation of hyperuricemia in nongouty patients (discussed in previous Reviews) were further clarified by application of modern methods of genetic analysis.[1875] Smyth, Cotterman and Freyberg[1874] analyzed data on 87 relatives of 19 men with gout, and found hyperuricemia to be transmitted apparently by a single dominant autosomal gene which is not sex-linked; only a portion of the heterozygotes for this factor developed gouty arthritis. Stecher, Hersh and Solomon,[1929] studying 201 members of 44

gouty families, also found their data to fit the theory of a single autosomal gene, with estimated penetrance of 84 per cent in the heterozygous male and 12 per cent or less in the female relatives. Age seemed to be an important factor, as familial hyperuricemia was not present in males under the age of 16,[1874] or in women until after the menopause.[1929] [The hereditary transmission of the biochemical abnormality characteristic of gout appears to be definitely established. Still unanswered is the question of what factors determine whether an individual with hereditary hyperuricemia will develop clinical gout.—Ed.]

Pathogenesis of Hyperuricemia. Theories explaining the mechanism of hyperuricemia were: overproduction of uric acid in the body, diminished destruction of uric acid in the body or decreased renal excretion of uric acid. "Conclusive experimental proof in support of any one of these three hypotheses is lacking" (Talbott). [Studies with labeled uric acid have reopened the possibility that uric acid may be destroyed in the body,[126, 127] and have not settled the question of whether overproduction of uric acid is responsible for the hyperuricemia of gout. These studies are discussed in detail under "The Uric Acid Problem."—Ed.]

Urinary output of 17-ketosteroids was found to be uniformly diminished in 11 gouty patients both during acute attacks and during asymptomatic intervals.[2208] Others have reported similar findings.[440, 1075, 1702] No evidence of altered metabolism or faulty excretion of androgens was found in gouty patients, nor was there evidence of androgenic deficiency. It was postulated, therefore, that androgen activity in gout may be maintained by an abnormal androgen, presumably of adrenocortical origin, which is metabolized without significant production of 17-ketosteroids. It was reported that males and females show differences in urate metabolism which appear at puberty,[2211] and that the renal clearance of urate was decreased in children following administration of testosterone.[2204] These observations suggested that normal urate metabolism is under the control of androgenic steroids, and that a hypothetic "gouty androgen" may be responsible for hyperuricemia, both in gout and in familial hyperuricemia.[2204] [Observations on the 17-ketosteroid excretion in nongouty persons with familial hyperuricemia have not been reported. Confirmation is needed of the observations upon which this interesting hypothesis is based.—Ed.]

Pathogenesis of Acute Attacks. The onset of acute gouty attacks after withdrawal of ACTH, in addition to the improvement frequently observed in patients with gouty arthritis after administration of ACTH, suggested a relationship between the state of adrenocortical function and the occurrence of acute attacks. The metabolic responses of one gouty patient to ACTH administered during a symptom-free interval were compared with those of normal subjects under identical conditions. The gouty patient developed an acute attack on the second day after ACTH withdrawal, at which time his metabolic picture indicated depressed adrenocortical function; in contrast, the metabolic picture of the normal subjects on the second to fifth day after ACTH was discontinued suggested a rapid return or "rebound" of endogenous adrenocortical activity.[1702] Other workers obtained evidence of decreased adrenocortical activity at the time acute attacks developed after withdrawal of ACTH.[841, 842, 2204] [Convincing evidence of such a change has not been reported in spontaneous attacks of gout.—Ed.] The entire "gout cycle" of electrolyte and water changes, which had been observed with spontaneous acute attacks of gout, was reproduced by administration and withdrawal of ACTH. As was true in spontaneous gout, some subjects did not develop an attack even though the electrolyte changes did occur.[841, 842]

While such observations led some workers to postulate that acute attacks of gout result from a defective response of the gouty patient to a deficiency of adrenocortical steroids,[2204] others did not agree. An acute attack was induced in only one of eight

patients after administration of ACTH during symptom-free intervals.[740] Patients treated for acute attacks with ACTH experienced recurrences after its withdrawal if colchicine was not given concurrently.[740, 1702, 1896, 2023, 2055] To Gutman and Yu such exacerbations suggested reëxhibition of the underlying disease when the nonspecific suppressive effect of ACTH was removed, rather than initiation of a new attack of acute gout. They concluded that "available evidence does not appear to justify the view that the pituitary and/or adrenal glands play a central rôle in the pathogenesis of gout."[740] [Further observations on the consistency with which gout can be provoked by ACTH withdrawal, and on the details of differences in metabolic effects of ACTH on normal and gouty subjects, will be necessary to establish or disprove the rôle of endocrine dysfunction in gout.—Ed.]

Another suggestion was that acute attacks are "associated with an increase in the ratio of bound urate to ultrafiltrable urate" in serum.[13] Observations made on one patient were compatible with this theory.

Laboratory Data. Liver function and serum proteins were normal in 43 patients with uncomplicated gout. Serum cholesterol values and partition were usually normal; total cholesterol values were significantly lower in acute gout than during symptom-free intervals, and were said to be highest just before the onset of gouty arthritis.[2206] Sedimentation rates were normal in seven of 30 patients during an acute attack.[1339] The rapid return of the sedimentation rate to normal as the acute attack subsided was sometimes helpful in the diagnosis of atypical cases.[885]

Blood Uric Acid. Serum determinations seemed preferable to those on whole blood. Recovery of uric acid from serum was more complete and more consistent than that from whole blood.[132]

In the course of genetic studies, data were obtained which define more accurately the limits of normal serum urate values. Analysis of 1,272 determinations, made by the direct method of Benedict, led Stecher, Hersh and Solomon[1929] to place the upper limit of normal at 6.5 mg. per 100 c.c. for men, and 6.0 mg. per 100 c.c. for women. Smyth, Cotterman and Freyberg,[1874] using the indirect method of Folin, found the upper limit of normal to be 6.0 mg. for men and 5.0 mg. for women. The difference in blood and plasma urate levels between normal men and women was statistically significant, and the ratio of values in women to those in men averaged 0.84.[132, 1874, 1875, 2211] The values in gouty women were also generally lower than in gouty men. This difference between the sexes was not found in normal children, and was believed to develop at puberty.[2211] Factors of age and sex may be important in determining the time of appearance of hereditary hyperuricemia, and possibly of clinical gout.[1875]

Pathology. The unique and specific features of gouty granuloma were illustrated. Histologic features are the same in different sites, such as the cartilages of the ear, the olecranon bursae, the kidneys, and various parts of the joints. The lesion was thought to originate as a localized region of necrosis resulting from deposition of urate crystals, with an ensuing foreign body reaction. Synovial membranes reacted to the presence of these granulomata by thickening and pannus formation which, in essence, does not differ from that observed in rheumatoid and tuberculous arthritis, except for encrustation with urates.[1726] In osseous tophi, the deposition of urate crystals was believed to inhibit the action of osteoblasts.[1957, 1958]

Kidneys. Some kidneys were sclerotic, others were sites of infection. Urate deposits were found in the medulla and the inner part of the cortex, where they appeared to be located in the interstitial tissues and not in the tubules.[1078, 1902] It was

suggested that the urates were originally deposited in the tubules, but that inflammation and reaction to the urates had destroyed the tubular structure.[231] Thirty to 50 per cent of patients died of renal disease[2020]; this was the most important cause of death, irrespective of age.[2021]

Diagnosis. With few exceptions,[1478] diagnosis followed accepted criteria, with emphasis on the clinical characteristics of attacks, the presence of hyperuricemia, and the therapeutic response to colchicine. The response of acute attacks to adequate dosage of colchicine was considered specific for gout, and so consistent that it had diagnostic value as a therapeutic test.[2019] It was again emphasized that roentgenograms often show no abnormality early in the disease, and that the x-ray findings are usually not pathognomonic.[267, 654, 2019] Opinions continued to differ as to the consistency with which hyperuricemia can be detected early in the course of gout. "The concentration of serum urate in gouty persons is elevated irrespective of the presence or absence of acute joint symptoms. The determination should be done on serum or plasma rather than whole blood. Most patients with gout show a concentration of uric acid above 6 mg. per 100 c.c., and most nongouty have a concentration below 5 mg. Gouty patients may have a normal value immediately following salicylate or cinchophen therapy. If a border-line value is obtained initially, the determination should be repeated one or more times" (Talbott[2019]). [We would add ACTH, cortisone, Benemid and phenyl butazone to therapeutic agents capable of lowering the serum urate.—Ed.]

[Those of us working in centers where careful attention can be given to uric acid determinations rarely encounter normal values in patients with gout. This is true when determinations are made on serum, when the range of normal values by the method employed has been accurately defined, and when the effect of medication on the serum urate levels is excluded. In contrast, those of us who have to rely on the usual laboratory facilities, especially when the determination is made on whole blood, find an appreciable number of patients with normal values. Certainly the diagnosis of gout should not be ruled out on the basis of a single normal value.—Ed.]

Treatment. *Acute Attacks.* The usual principles, relying on early and adequate use of colchicine, rest and liberal fluid intake, were restated. With colchicine, improvement was rapid in 37 of 44 attacks. Cinchophen seemed effective in some colchicine-resistant patients.[1339] Successful therapy was said to depend on beginning colchicine at the very first warning and using enough to produce some nausea or a loose bowel movement.[1169] [While it may be necessary to give colchicine to tolerance in full-blown established attacks, if it is used early during the development of acute gout a good effect can be obtained without toxic symptoms.—Ed.] In addition to colchicine and a high carbohydrate diet, 500 c.c. of 20 per cent glucose were said to give striking benefit; it was injected intravenously twice the first day and once for the next two or three days.[99] X-ray therapy over inflamed joints may be helpful in stubborn cases.[601]

Hellman[841] was apparently the first to observe the striking clinical improvement afforded by ACTH in acute gout. Its value has been confirmed by many others.[740, 1193, 1295, 1348, 1702, 1896, 2023, 2085, 2210] "Most important was the recognition that if colchicine is not given simultaneously with ACTH or shortly thereafter, the subsidence of symptoms may be followed by an exacerbation of acute joint distress."[2023] In one series, ACTH was reported to have terminated all of 51 attacks quickly, even those resistant to colchicine and other measures.[2210] In another series the response of acute

gout to ACTH was considered satisfactory in only seven of 11 patients,[740] and patients have been observed who did not respond to ACTH but did respond to colchicine.[2023] Termination of acute attacks by means of whole adrenal cortical extract [2210] and cortisone [176, 1157] was also reported. Others found cortisone ineffective.[1157, 1348, 2210]

[It seems probable that colchicine will remain the sheet-anchor in the treatment of acute gout, as it will satisfactorily control the majority of acute attacks. Several of us have found the use of ACTH another effective method of control, particularly welcome in the management of unusually severe or colchicine-resistant attacks, or where prompt suppression of distress is required.—Ed.]

Interval Treatment. There was general agreement that the diet should eliminate high purine foods and that obese patients should be reduced. The patient should understand the nature of the disease and the factors which tend to provoke attacks.[601, 1169] Abstinence from alcohol [99] and moderation in use of alcohol [601] were recommended. The use of maintenance doses of colchicine, one to three tablets daily, appeared to be increasing in popularity. [The ability of colchicine to prevent ACTH-withdrawal attacks, particularly after the use of ACTH in treatment, is the best evidence available that maintenance colchicine may be of prophylactic value. Some of us are not impressed with the value of "maintenance colchicine" to prevent attacks.—Ed.] Intermittent administration of salicylates was advised.[99, 601, 1169] No improvement was noted in two patients during administration of testosterone propionate.[784]

"There should be no hesitation in the removal of subcutaneous tophi, the excision of discharging tophi, or the removal of functionless fingers or toes" (Talbott [2023]). "In the prevention and treatment of chronic tophaceous gout, the use of ACTH is neither feasible nor desirable at present" (Gutman [740]).

Studies of Colchicine. The mode of action of colchicine in gout did not appear to be the release of ACTH.[740, 2204] The possibility of its action through the vasomotor nerves was recalled.[1002]

An instance of fatal colchicine poisoning was reported, and four other cases were reviewed. A 39 year old man with atypical rheumatoid arthritis (confirmed by histologic examination) and an unusual degree of lymphadenopathy had received a total of 6 mg. of colchicine over a three-day period, when he abruptly complained of nausea and colicky abdominal pain. Vomiting, diarrhea and coma followed, and the patient died two days later. At autopsy, the lymph glands showed generalized necrosis with absence of mitotic figures. The spleen was extremely congested. Since in all five cases the fatal outcome had followed a total dose of 13 mg. or less of colchicine, it was difficult to explain these cases as "other than very rare examples of hypersensitivity to colchicine." [1274]

Cinchophen Toxicity. One death was reported as probably related to cinchophen.[1191] A 59 year old woman with chronic rheumatoid arthritis died 12 days after taking 2 gm. of cinchophen. At postmortem examination the liver was very small, with severe toxic necrosis of cells, and there were calcium casts in the kidney tubules in addition to cholemic nephrosis. Five cases of agranulocytosis related to cinchophen were reviewed and a sixth was added.[1952] The patient had taken 1.5 gm. of cinchophen daily for one month because of muscular rheumatism before becoming ill with a severe sore throat. The blood count revealed 1,200 leukocytes with 3 per cent neutrophils. This patient made a good recovery.

An excellent review of cinchophen and its derivatives appeared (Hueper). It was recommended that their use for treatment of ordinary colds, headaches, neuritis and similar conditions should be entirely discontinued, as the risk entailed by the disease does not justify the administration of an agent with serious hazards. On the other hand, the use of cinchophen and its derivatives, with the exception of the iodine-containing compounds, should be continued in the management of gouty arthritis and other rheumatic diseases that cannot be satisfactorily controlled with less dangerous drugs.[945] [The reports of cinchophen toxicity since 1932 were summarized in the Ninth Rheumatism Review. It was emphasized that most instances of toxicity have developed in patients with rheumatoid arthritis. We would reserve the use of cinchophen for patients with gout in whom the disease cannot be controlled with other measures.—Ed.]

Uric Acid Problem

Precursors of Purines and Uric Acid. By administering a variety of isotopically labeled compounds and identifying the isotopic tracer in various positions in excreted uric acid or in purines isolated from tissues, the metabolic precursors of uric acid have been identified as relatively simple compounds readily available from the "metabolic pool." The information regarding sources of the various atoms of the purine molecule is summarized in figure 1 and table 8. The studies indicate that precursors are the same in birds, rats and man. Arginine, histidine, pyrimidines and urea are not used in the formation of uric acid.[1889] It seems likely that glycine is the nucleus around which other carbon and nitrogen atoms become associated in the biosynthesis.[1818] [These results would appear to

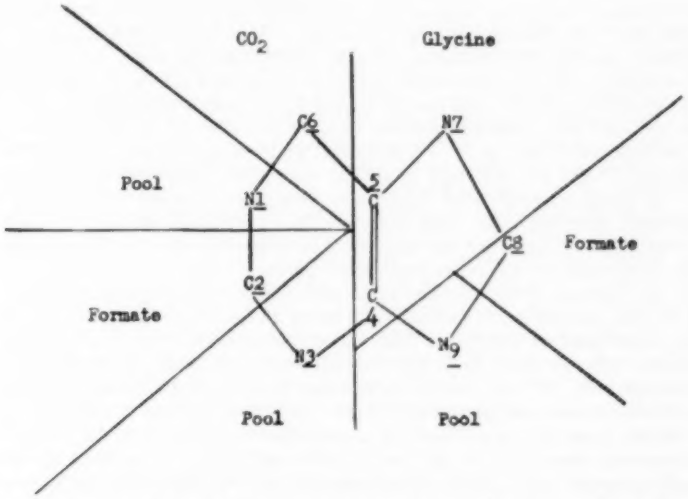

FIG. 1. Sources of the various atoms of the purine molecule. (Reproduced from p. 689, *in* G. G. Duncan, Diseases of Metabolism, 3rd Ed., 1952, through courtesy of Dr. Walter Bauer and W. B. Saunders Company.)

TABLE VIII

Sources of Various Atoms of the Purine Molecule

	Source	Reference
Nitrogens 1, 3, 9	Amino nitrogen of metabolic pool	92
Nitrogen 7	Glycine	6, 1818
Carbons 2 and 8	Formate or compounds yielding one carbon compound	503, 836, 1037, 1889
Carbon 4	Carboxyl group of glycine	243, 836
Carbon 5	Methylene carbon of glycine	1037
Carbon 6	Carbon dioxide	836, 1889

preclude the possibility of influencing the precursors of endogenous uric acid by dietary regulation.—Ed.]

Studies with Labeled Uric Acid. Availability of uric acid labeled with the heavy isotope of nitrogen (N^{15}) has permitted the determination of the fate of injected uric acid in man, and the estimation of the magnitude of over-all urate metabolism in normal and gouty subjects. Of distinct advantage is the fact that "physiologic" doses of uric acid, ranging from 50 to a few hundred milligrams, can be used.

After oral ingestion of labelized uric acid, 72 per cent of the isotope was accounted for in the urine within three days. Only 27 per cent of the dose was recovered as unchanged uric acid; the remainder had been degraded to urea or ammonia, presumably in the gastrointestinal tract. In contrast, after intravenous injection all of the isotope was in the form of uric acid; 88 per cent of the dose was recovered in three days, 95 per cent in five days.[631]

The rate of urinary excretion of N^{15} after intravenous injection follows a logarithmic decay curve, from which it is possible to calculate the amount of uric acid in the body with which the labeled material has mixed. This is termed the miscible pool. The turnover rate, i.e., the amount of uric acid which enters or leaves the pool per day, can be calculated from the quantitative excretion of labeled uric acid if it is assumed that the size of the pool does not change during the period of observation. In normal subjects, pool size was estimated variously at less than 1,000 mg.,[631] from 1,100 to 1,300 mg.,[126] and less than 1,500 mg.[2022] The normal turnover rate ranged from 0.52 to 0.76 pools per day,[126, 2022] or, expressed in another way, the half-life of the pool was 0.85 days.[631] In gouty subjects, pool size was consistently increased to from two to 30 times normal. Absolute values ranged from 1,900 mg.[2022] to 31,019 mg.[127] The turnover rate expressed in pools per day was less than in normal subjects, although absolute values in milligrams per day were often much higher.

The distribution of the miscible urate pool within the body was calculated. In normal subjects, plasma water accounted for about 20 per cent. If the remainder were uniformly distributed in nonplasma body water, the concentration of uric acid in this compartment was calculated to be approximately one-half of the concentration in the corresponding sera. When similar calculations were applied to gouty subjects, the plasma and body water compartments fell far short of accounting for all the uric acid in the miscible pool; it was necessary to assume that a portion of the uric acid in the solid phase (not necessarily in well-established tophi) was in equilibrium with uric acid in solution, and constituted a compartment of the miscible pool. In a tophus excised on the ninth day after injection of labeled uric acid, the isotope content decreased progressively in serial extractions which apparently removed successive laminae of uric acid from its surface.[126, 127]

In normal subjects, the calculated quantity of uric acid introduced into the miscible pool daily exceeded the urinary excretion by 110 to 250 mg. per day. Losses in feces and sweat were not investigated. Likelihood that a portion of uric acid undergoes degradation was suggested by the finding of small concentrations of isotope in urinary urea and ammonia.[126] Intestinal flora acting on uric acid excreted into the gut may be responsible for such degradation.[127] Similar calculations could not be applied to gouty subjects, as the contribution to the miscible pool from uric acid in the "solid phase" could not be distinguished from newly formed uric acid.

In a patient with severe tophaceous gout, the miscible pool was decreased from 31 gm. to 2 gm. following uricosuric doses of acetylsalicylic acid for about four months.[127] Decrease in pool size and increased rate of turnover were observed after administration of cortisone and of ACTH to gouty patients.[2022] In one study, full doses of colchicine resulted in decrease in pool size and increased turnover rate[2022]; in another subject, studied under different conditions, colchicine had no demonstrable effect on the quantities measured.[127]

[The authors of these reports have emphasized the preliminary nature of the conclusions drawn. In the reports reviewed, a total of seven gouty and 11 nongouty subjects have been studied. The assumptions underlying treatment of data and calculations have been clearly stated. The possibility that there are two phases of equilibrium for injected uric acid—a rapid equilibrium persisting for 24 to 30 hours which merges with a second, more stable phase—presents a problem which has not been solved. Nevertheless, this method is yielding fundamental information not accessible by other methods, and further work can be expected to clarify many aspects of uric acid metabolism.—Ed.]

Methods of Determination. *Blood.* A colorimetric determination of serum uric acid with alkaline ferricyanide was described.[1845] The enzymatic method previously applied to urine, by which "true uric acid" is determined by the difference in color production after destruction of uric acid by uricase, was applied to blood. "True uric acid" accounted for an average of 85 to 90 per cent of total chromogenicity of whole blood and of serum.[161] The cerebrospinal fluid was found to contain only one tenth of the ultrafiltrable fraction of plasma.[2213]

Urine. Artifacts are found when the uricase method is applied to urines containing glucose,[149] or after salicylate administration.[2246] These are due to instability of glucose and gentisic acid in the alkaline buffer required during the period of uricase action, and can be eliminated by simple measures. Values by a colorimetric method averaged 1.16 higher than those obtained by the isotope dilution technic.[631]

Physiology. *Human.* The marked increase in uric acid excretion which follows ACTH or cortisone administration has suggested an endocrine regulation of urate metabolism. This phenomenon, first reported by Forsham et al.,[577] has been carefully studied by several groups.[339, 576, 740, 854, 2056] Adrenal corticosteroids of the 11 or 11–17 oxygenated types are the effective agents. Serum urate levels usually decrease in both normal and gouty subjects as the urinary excretions increase. When ACTH was administered a few days after infusion of labeled uric acid to normal and gouty subjects, there was no change in the rate of decline of excretory isotope values.[127] This supports other evidence[740] suggesting that the uricosuria produced by adrenocortical stimulation is largely the result of increased renal clearance of uric acid.

In further studies on the renal mechanism of urate excretion, there was general agreement that normal urate clearance in man is only 8 to 10 per cent of the glomerular filtration rate. Most workers continued to accept the concept of complete glomerular filtration of plasma urate with active tubular resorption, and explained uricosuric phenomena on the basis of alteration in tubular resorption.[607, 608] An alternative hypothesis that a large portion of the plasma urate is not filterable through the glomerulus (proposed by Berglund and Fisk in 1935) was supported by Wolfson and associates, who suggested that the major portion of the plasma urate circulates as polymeric urate

complexes.[1204, 2212] Simultaneous inulin and urate clearances were determined during intravenous loading tests on four normal subjects. Over a range of plasma urate levels as high as 19.1 mg. per 100 ml., the maximal tubular resorption (Tm) for urate was in the order of 15 mg. per minute per 1.73 M^2, and was reproducible from time to time in a given subject. "The magnitude of the Tm is such that it is almost certainly never saturated under physiologic conditions." [136] Glycine and salicylates increased urinary urate excretion.[607, 608] Urate clearance was more than doubled when the blood glucose was maintained at 500 mg. per cent or more by intravenous infusion.[185] Uricosuric effect was noted promptly following administration of caronamide.[2205] [This observation led to the utilization of another tubular blocking agent, benemid, for its uricosuric effect.—Ed.] An interesting patient with hypouricemia was carefully studied. Plasma urate values ranged from 0.2 to 0.6 mg. per cent, while the concentration of oxypurine precursors of uric acid in the plasma was five times the normal values. Urinary urate excretion was normal, resulting in a tenfold increase in urate clearance. Since urate clearance averaged 150 per cent of inulin clearance, in this person "uric acid is either excreted by tubular secretion, or is formed in the kidney." [1599]

The nature of the chromogen in body fluids which is not destroyed by uricase was investigated. It appeared to be endogenous in origin, and changes in blood and urine levels in both man and animals tended to parallel those of "true urate" under a variety of conditions. No non-urate chromogen was found in a gouty tophus. The ratio of "true urate" to total chromogen was said to be constant enough to make it unnecessary to use the uricase method for clearance studies.[2209] [An obvious exception to this statement is seen when such studies are carried out during administration of salicylates.—Ed.]

Animals. The anomalous production of uric acid in the Dalmatian dog was reinvestigated. When both end-products of purine metabolism (allantoin and uric acid) were considered, the total production and excretion of purine metabolites were equal to those of other breeds of dogs. In one study, urate excretion was found to be at the exact level of glomerular filtration rate, indicating no tubular resorption of urates.[609] Others, using the uricase method, found urate cleared at a rate considerably greater than that of glomerular filtration, indicating its excretion by both glomerular filtration and active tubular secretion.[2207]

Purified and relatively stable uricase was prepared in lyophilized form. It was effective in temporarily lowering the blood urate levels in chickens, but its repeated use led to mild anaphylactic reactions.[29]

(*To be concluded in October issue.*)

CASE REPORTS

HEMOLYTIC ANEMIA SECONDARY TO MESANTOIN*

By Isidore Snapper, *Chicago, Illinois,* Dorothy Marks, Lawrence Schwartz, and Lester Hollander, F.A.C.P., *New York, N. Y.*

The diagnosis of acquired hemolytic anemia secondary to autoantibodies is being made with increasing frequency in recent years. In large part this is due to the recent availability of new technics for detecting this group of disorders, and for separating these cases from other varieties of hemolytic anemia, more particularly from the hemolytic blood disorders of congenital origin.[1] In this regard the presence of a positive Coombs' test is generally considered to be of paramount importance in establishing the diagnosis of acquired hemolytic anemia.[2] Included in this group of acquired hemolytic anemias with autoantibodies are those cases secondary to various malignant diseases,[3] and those poorly defined but frequent cases of unknown etiology usually called idiopathic hemolytic anemia.

It is the purpose of the present paper to report a case of acquired hemolytic anemia with antibodies in an otherwise healthy 60 year old male with petit mal, in whom it seems highly likely that the hemolytic process was secondary to therapy with mesantoin. The case is of interest in that, although mesantoin has been implicated in other blood dyscrasias, this is the first report of its playing an etiologic rôle in a case of hemolytic anemia. It is also the first known report of a positive Coombs' test with autoagglutinins and panagglutinins in a drug-induced hemolytic anemia.

Case Report

A 60 year old male was first admitted to the Mount Sinai Hospital February 2, 1952, complaining of weakness, fever and anorexia of one week's duration. Family history and personal history were negative. Past history revealed the occurrence of momentary episodes described as a loss of contact with his surroundings, when he would lapse into German, a language he had used only in his childhood. These episodes had commenced 20 years prior to admission, occurred at intervals of from two months to two years, and were never accompanied by any abnormal movements, loss of consciousness or incontinence. For the past four months he had been placed on mesantoin, 0.4 gm. once a day, on which regimen attacks still recurred.

The present illness may be said to have begun two months before admission, at which time the patient developed a temperature of 101° F., associated with a nasal furuncle. He became afebrile after one day of penicillin therapy. Two weeks later he again became febrile, with no associated constitutional symptoms, and was again treated with penicillin, resulting in defervescence and the appearance of an urticarial eruption which subsided over the following week. One week before admission temperature again rose to 101° F.; this time there were associated anorexia, nausea, weakness and weight loss of approximately six pounds. In addition, the patient noted

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the appearance over his forearms of several pea-sized macular areas, nonpruritic in nature. Physical examination revealed a very pale, chronically ill male with slight scleral icterus. There were several reddish macules, 1 cm. in diameter, spread over the trunk and, in addition, a fine purplish red reticular discoloration over the trunk and extremities, blanching on pressure. Temperature was 101° F.; blood pressure, 110/80 mm. of Hg; pulse, 112; respirations, 12. There was no generalized adenopathy. Mucous membranes were pale but clear, save for cheilosis. The lungs were clear. The heart was slightly enlarged to percussion, the sounds were of good quality, with a grade II apical systolic murmur, not transmitted. The liver was enlarged two fingerbreadths below the right costal margin and was firm and nontender. The spleen was palpated one and one-half fingerbreadths below the left costal margin and was soft and nontender. The prostate was enlarged to twice normal size and was of moderately firm consistency.

TABLE I

	2/2	2/5	2/12	2/15	4/15
Hemoglobin	4.8	12.7	8.5	12.0	16.0
Red Blood Cells	1.27	4.5	3.8	3.7	5.3
White Blood Cells	8450	2700	4050	5100	8000
Blasts		2			
Myelocytes		18			
Segmented	22	25	34	60	
N. Segmented	24	25	1	5	
Monocytes	11	14	22	11	
Lymphocytes	47	25	23	24	
Eosinophils					
Basophils					
Plasma	2				
Reticulocytes		17	3.9	0.2	0.3
Platelets		18,000	150,000	130,000	
Marrow	Erythroid Hyperplasia		Erythroid Hyperplasia		Normal Marrow
Coombs'					
Direct	3+	3+	3+	2½+	0
Indirect	+	+	+	0	0
Trypsin					
Agglutination	4+	4+	4+	4+	0
Plasma Hemoglobin	3+	3+	2+	0	
Methemalbumin	2+	+	Tr.	0	
Icteric Index		30	12	6	
Urine					
Urobilinogen	1/1280	1/1280	1/80	1/80	

The patient's course during his two week hospital stay can best be followed with reference to table 1. It should be noted that on admission he presented clinical and laboratory findings diagnostic of hemolytic anemia, as evidenced by pallor, icterus, splenomegaly, a blood smear showing spherocytosis, polychromatophilia and nucleated red blood cells, positive Coombs' test, free plasma oxyhemoglobin and methemalbumin, increased urinary urobilinogen and hemosiderin, and an erythroid marrow. Depression of the other blood elements in the marrow could not be demonstrated because of this extreme erythroid reaction. Additional admission findings not charted included negative electrocardiogram, chest x-ray and bone films, negative blood preparation for lupus cells, serum albumin ranging from 3.3 to 4.0 gm./100 c.c., serum globulin 4.0 to 4.4 gm./100 c.c., negative Wassermann, negative heterophil agglutination, alkaline phosphatase of 7 King Armstrong units, and cephalin flocculation varying from 2 to 3 plus throughout the patient's hospital stay.

It was observed on admission that the patient's cells agglutinated spontaneously in his own serum. Tests for cold agglutinins and cryoglobulins were negative. Upon cross-matching the patient's blood (patient being Type B, Rh′ + Rh° + Rh″ −), it was observed that a panagglutinin was present in addition to a type specific antibody for Rh″ cells.* Despite this, the patient could be transfused fairly uneventfully. As can be seen in the table, over the course of his first three hospital days he received five transfusions, to which he made a favorable response, his hemoglobin rising to 12.7 gm. from an admission level of 4.8 gm. At this time further blood studies revealed the presence of a severe leukopenia (2,700 white blood cells/cu. mm.) and a thrombopenia (18,000 platelets/cu. mm.) concomitant with a bleeding time of 15 minutes, clotting time and clot retraction being within normal limits. Hemolytic activity continued, as evidenced by increased urinary urobilinogen. (Quantitative studies at this time showed 235 mg. urinary urobilinogen excreted in 24 hours.) Fecal urobilinogen studies done somewhat later, when hemolytic activity was not so intense, showed 198 mg. excreted over a 24 hour period. Reticulocytosis of 17 per cent was present, and free blood pigments continued to be present in the plasma. The abnormal antibodies seen on admission likewise persisted, and over the following week the patient showed a decrease in hemoglobin to 8.5 gm., with a persistent moderate reticulocytosis, while his white cells and platelets came back to normal levels. Red cell fragility studies at this time revealed moderately increased fragility, with complete hemolysis at 0.0 to 0.32 per cent saline, partial hemolysis at 0.36 to 0.52 per cent, and no hemolysis at 0.56 to 0.72 per cent. At this point, further studies were begun to determine the rate of blood destruction, and on February 14 the patient accordingly was transfused with three units of packed O cells, following which daily bloods were drawn for cell survival studies by a modified Ashby technic,[5] which showed a normal cell survival.

At the end of a six week period of observation evidence of increased blood destruction had disappeared, hemoglobin was maintained between 12 and 13 gm., reticulocytes and urobilinogen fell to normal levels, blood pigments disappeared from the plasma, and red blood cell fragility became normal. In addition, the immunologic mechanisms reverted in that the indirect Coombs' and type specific antibody disappeared after two weeks, while the direct Coombs' and trypsin agglutination fell serially in titer, disappearing at four weeks (table 2). Symptomatically, prior to discharge the patient's strength returned, his appetite improved, the skin eruption disappeared. The spleen was no longer palpable by the end of the first hospital week. During the second hospital week the patient had a transient episode of pleuritic type pain in the left lower chest field posteriorly, associated with a small patch of bronchovesicular breath sounds over this area, which cleared in several days. Chest x-ray findings were negative. When seen six weeks after discharge the patient was completely afebrile and asymptomatic and engaging in his usual activities.

In summary, therefore, we have a patient with a self-limited episode of acute hemolytic anemia, probably secondary to drug therapy, associated with an autoagglutinin and panagglutinin, spherocytosis and evidence of intravascular blood destruction, all of these manifestations reverting toward normal on purely supportive therapy, i.e., blood transfusions, within a four week period.

* The antibodies were studied by observing the agglutinative effect of the patient's serum both on unaltered and on trypsinized red cells (both Type O, Rh neg., and others of known antigenic constitution). The red cells were trypsinized by the method of Rosenfield.[4] Direct and indirect Coombs' tests were performed by conventional technics.[2] Agglutinin titers were established by the method of twofold serial dilution using saline diluent and trypsinized type O Rh − red cells as substrate. Incubations were for one hour at 37° C. and agglutinations were read both micro- and macroscopically. The panagglutinin was characterized by an insignificant variation in titer with variation in temperature, and was of the incomplete type, i.e. did not cause agglutination of unaltered cells in saline media.

TABLE II
Panagglutination Titer*

Date	Dilutions of Patient's Serum				
	1:2	1:4	1:8	1:16	1:32
2/2	4+	4+	2+	1+	0
2/3	4+	4+	2+	±	0
2/4	3+	2+	1+	0	0
2/6	3+	2+	1+	0	0
2/7	3+	1+	±	0	0
2/9	2+	1+	±	0	0
2/17	2+	±	0	0	0
3/6	0	0	0	0	0

* Measured against trypsinized cells—see text.

DISCUSSION

Mesantoin (3 methyl 5.5 phenylethyl hydantoin) has been used rather widely for the last five years in the treatment of epilepsy.[7] Kozol [6] has reported a 15 per cent incidence of hematologic side effects, i.e., leukopenia, occurring usually one to three months after the onset of administration of the drug. Abbott and Schwab [8] reported 11 cases of pancytopenia, with six deaths occurring after an asymptomatic period of from three to nine months. In none of these cases was there any evidence that a hemolytic process was present in addition to the toxic depressant effect on the blood elements. Other less serious side effects reported after the administration of mesantoin include cervical adenopathy, fever, drowsiness and morbilliform rash.

In the case under discussion is seems most likely that the acute self-limited process of pancytopenia, with the added feature of an acquired hemolytic anemia, was due to mesantoin. The only other drug that could be implicated by history was penicillin, and review of the literature reveals no clear-cut cases of either hemolytic anemia or pancytopenia secondary to this drug. Spring [9] and Anderson [10] have reported cases of nonthrombocytopenic purpura after the administration of penicillin; and Moraques and Wyatt [11] have presented a case of lower nephron nephrosis and hemoglobinemia, after intrathecal administration of penicillin to a syphilitic patient. This reaction they believed due to an immunologic mechanism secondary to preformed cold hemolysins 2° to the lues, though they were not demonstrated in the case under discussion. Spain [12] presented a case of agranulocytosis concomitant with penicillin therapy which, however, the author himself felt was not sufficiently conclusive.

The other point of interest presented by this case is that of the nature of the antibody responsible for the acute hemolytic process. Hemolytic anemias have been reported secondary to numerous other drugs, e.g., sulfadiazine [13] et al., but in none of these cases were there any abnormal antibodies that could be demonstrated to be responsible for the causation of the hemolytic process, which was believed to be due either to a direct or to an indirect effect of the toxic substance on the red blood cell. In this case the presence of at least two types of antibody whose titer could be correlated with the severity of the disease process was demonstrated.

The intimate mechanism by which the antibody of acquired hemolytic anemia is formed is as yet unknown. It can be conceived that minor alterations in the structure of the red blood cell may impart new antigenic properties to it. Such a new antigen could then immunize the patient against the altered red blood cell. If the autoantibody thus produced were of relatively low specificity it might affect normal red blood cells as well. Many examples of heterogenetic response to antigenic stimulation are known, and this subject has recently been reviewed by Weiner,[14] who invoked such an explanation to account for the occurrence of some naturally occurring agglutinins. It is possible to conceive, therefore, that whereas some drugs may injure the red blood cell directly without an intervening antibody mechanism, in other cases the mechanism described above may be invoked. Subsequently, with the discontinuance of the antigenic stimulus, antibody titer would then fall off to the point of actual disappearance.

Summary

1. A case is presented of acquired hemolytic anemia and pancytopenia associated with the presence of abnormal antibodies. The etiologic factor is believed to be mesantoin.

2. The toxic effects of mesantoin are reviewed.

3. A hypothesis for the mode of production of the abnormal antibodies is presented.

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BLACK WIDOW SPIDER (*LATRODECTUS MACTANS*) POISONING TREATED WITH D-TUBOCURARINE CHLORIDE * †

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THE clinical syndrome following Black Widow Spider bite is well recognized and consists chiefly of rather insignificant pain in the area of the bite, followed in a variable but usually short interval by severe systemic manifestations, characterized chiefly by pain and muscle spasm. The most commonly affected muscles are those of the abdomen and back. The venom is said to be a toxalbumin,[1] with its most damaging action on the nerve endings. Recovery is not accompanied by any known permanent neurologic damage.

In the following case it was felt that the origin of the patient's extreme pain was in the muscle spasm. Since curare has the ability to block nervous impulses at the myoneural junction and produce relaxation of spasm,[2] this appeared to be an ideal agent to use when more conservative measures failed to produce relief.

CASE REPORT

A 21 year old white airman was admitted to the hospital approximately six hours after being bitten on the scrotum while sitting in an outdoor latrine. He identified the arthropod by its characteristic appearance. The delay in admission was due to travel from an isolated area.

On entering the hospital the patient appeared acutely though not severely ill. He complained of moderate pain in the lumbar area of his back. This was evidenced by slight spasm bilaterally. There were no findings of significance in the area of the bite and there was no complaint of pain in this region. His pain and spasm rapidly increased over the next half hour. He was given 1 gm. of calcium gluconate intravenously and .015 gm. of morphine sulfate intramuscularly. One hour after the above injections his symptoms and signs were still increasing. The back was held in an opisthotonoid position, the muscles of the abdomen were rigid to the point of being boardlike, and there appeared to be slight interference with respiration due to tightness of the intercostals. It was then decided to use curare, and he was slowly given 60 units (9.0 mg.) of d-tubocurarine intravenously. (Weight of patient, 135 pounds.) Relaxation and relief of pain were striking and almost immediate. One and one-half hours later an ampule of *Latrodectus mactans* antivenom ‡ was obtained and this was given to the patient as an antagonist to any still-circulating and non-fixed toxin.

Four hours after the initial dose of d-tubocurarine he began to complain of a return of symptoms. An additional 60 units were placed in 1,000 c.c. of saline and given intravenously over the next three hours. The symptoms again promptly subsided and the patient remained asymptomatic save for slight muscle soreness noted the next morning. He was discharged the next day with no complaints.

COMMENT

This is the first use of curare (to our knowledge) in the treatment of this condition. It is believed to have been immediately successful in alleviating the

* Received for publication April 15, 1953.
† Tubocurarine Chloride Solution—Squibb.
‡ Lyovac—Sharp and Dohme.

severe signs and symptoms where the usual recommended procedures failed. The short duration and nature of the disease make it ideal for treatment with this drug. Only small amounts may be required. Diluting the drug into an infusion is a very satisfactory way of adjusting the dose to the symptoms and reaction. The usual precautions should be observed.

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NEUROPATHIC (CHARCOT) JOINTS OCCURRING IN DIABETES MELLITUS *

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THE occurrence of gross changes in the bones of the feet as a complication of diabetes mellitus has been described by Bailey and Root,[1] Joslin, Root, White and Marble,[2] Parsons and Norton,[4] Beidelman and Duncan [5] and others. The recognition of this type of lesion depends upon both clinical and roentgenologic observation. The lesion usually develops insidiously and during periods of uncontrolled diabetes. Signs and symptoms of a diabetic neuritis are usually prominent, while the circulatory status of the extremity may be unimpaired. Perforating ulcers without gross infection or gangrene are often noted. The involved foot is swollen but *painless*, even when bearing weight. On x-ray examination the characteristic appearance is fragmentation and lysis of the bones of the foot, especially the tarsal bones and proximal ends of the metatarsals. Callus formation is noticeably absent.

The bone changes which have been previously described and which will be further discussed in connection with this case report are believed to represent a manifestation of diabetic neuropathy.

Survey of the literature indicates that 30 such cases have been reported, and the thirty-first is herewith presented.

CASE REPORT

The patient is a 58 year old woman who now weighs 183 pounds and has always been considerably overweight. The diagnosis of diabetes was first made 17 years ago. During this period she has had many complaints relating to the feet and legs.

In July, 1945, a perforated ulcer associated with necrosis of the head of the fifth metatarsal of the *left* foot was noted. At that time the patient had good dorsalis pedis and posterior tibial pulses but there was considerable swelling of the foot. With careful control of her diabetes these lesions healed, the necrosis of the bone did not progress and, in fact, recalcification and bony repair occurred.

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From the Department of Internal Medicine, The Wheeling Clinic, Wheeling, West Virginia.

In June, 1950, she developed several blisters on the right foot accompanied by severe pain in the calf of the right leg. At that time there was marked swelling of the right foot and right leg, but the dorsalis pedis and tibial pulses continued to be excellent. A plantar wart was noted over the head of the second metatarsal.

The x-ray examination of the foot was reported as follows: "Examination of the right foot shows marked swelling of the soft parts of the foot. There is generalized bone atrophy seen and the head of the second metatarsal shows a decided loss of bone substance. Arthritic changes are noted about the tarsus. A bone spur is present at the insertion of the Achilles tendon (figure 1).

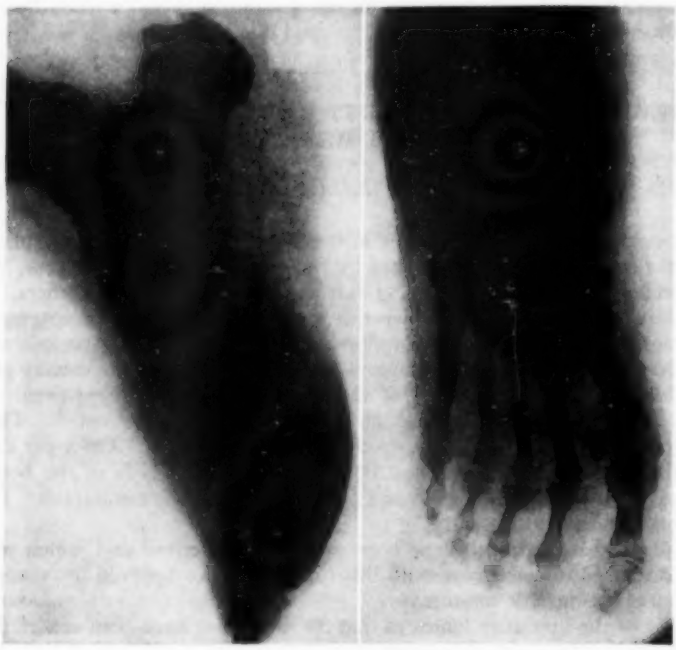

FIG. 1. Dorsal and lateral views of right foot, June 16, 1950. The process is just beginning in the distal end of the second and third metatarsals.

"X-ray diagnoses: Marked swelling, soft parts, right foot; bone destruction at head of second metatarsal with generalized bone atrophy."

The patient was admitted to the hospital and after appropriate preliminary studies a right lumbar sympathectomy was performed by Dr. C. D. Hershey. The supposed plantar wart revealed itself as a perforating ulcer in August, 1951, and drained persistently. There was a very persistent, thick callus around this area. During the next six months the ulcer healed and recurred at intervals while under treatment by a capable chiropodist. In spite of the large size and depth of the ulcer there has been no pain in the foot whatever and no evidence of gangrene or other signs of circulatory insufficiency. The patient walks without any real limp or apparent disability.

On reëxamination in June, 1952, we found that the ulcer on the sole of the right foot was somewhat larger and deeper and had a dusky red base. The ulcer exuded a nonpurulent serous exudate.

The foot was swollen especially on the dorsal surface. It continued to be painless and there was no evidence of skin or tissue discoloration suggestive of gangrene or cellulitis. The general physical examination was otherwise negative except for (a) obesity, and (b) a healed surgical scar in the right lumbar region. The circulation in the extremities seemed to be intact. However, an extensive diabetic

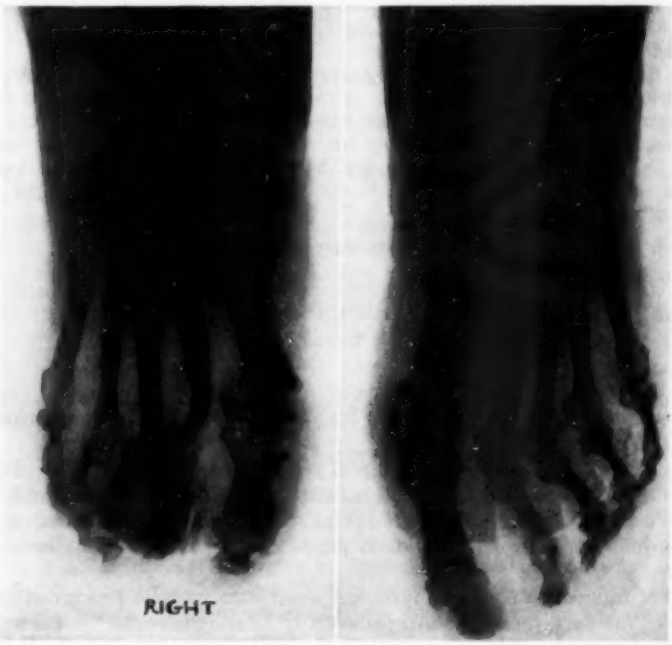

FIG. 2. Comparison of dorsal views of left foot and right foot, June 28, 1952. Note marked destruction and dislocation in distal ends of first, second and third right metatarsals as compared to the normal bones of the left foot.

retinitis had developed in the left eye and early cataract formation was noted in the right eye.

The neurologic examination was within normal limits except as follows:

1. Absent abdominal reflexes.
2. Markedly diminished patellar reflexes (elicited after repeated trial with strong reinforcement).
3. Diminution of sensitivity to pain and light touch over skin of right foot.

The examination of the spinal fluid was negative. The blood Wassermann test was negative, as were all other laboratory studies except for a blood sugar of 258 mg. per cent and a blood count (erythrocytes, 3,550,000; hemoglobin, 10 gm.; leukocytes, 9,400) indicative of a microcytic secondary anemia of moderate degree.

X-ray examination of both feet on June 28, 1952, was reported as follows: "Examination of both feet shows slight arthritic changes in the left foot. The right foot, however, shows marked changes. There is destruction seen at the head of the first and second metatarsals and destruction of the base of the proximal phalanx of the big toe and the second toe. The third toe is dislocated and there are also some slight destructive changes seen at the base of the proximal phalanx. Especially at the big toe, small bony fragments are lying inside of the area of bone destruction, between the fragments of the uninvolved bone.

"X-ray diagnosis: Suspicious for Charcot's disease, right foot." (Figure 2.)

The diabetes was readily controlled by a diet of carbohydrate, 170; protein, 85, and fat, 65, with 45 units of protamine insulin. The relatively low calorie diet was prescribed to attain further weight loss.

The involved foot was treated by conservative measures. Warm wet compresses were employed, alternating with periods of exposure to the infrared lamp to prevent waterlogging. The callus was gradually trimmed down and bed-rest enforced. The perforating ulcer began to fill in slowly but steadily and when the patient was last seen, in December, 1952, healing was well advanced. X-ray examination made on this date showed no essential change in the bone involvement as compared to the findings of June 28, 1952.

Discussion

The clinical and roentgenologic characteristics of the case reported are closely comparable to those previously described by other authors. Bone destruction in this patient is relatively slight in the tarsus but very marked in the first three metatarsals and the proximal phalanges. One is impressed by the appearance of lysis of the bones and the absence of any indication of bony repair or even any sign of calcium deposition. The bony fragments seem to be scattered around in a loose and irregular fashion.

This patient's foot exhibits no sign of cellulitis or other infection. There is eversion and marked thickening and a flattening of the longitudinal arch. Despite the marked deformity there is no pain. The other clinical entities (syphilis, syringomyelia and leprosy) known to produce Charcot-type joints were easily eliminated in our case.

It is of interest to note that lysis and absorption of bone proceeded steadily in spite of the performance of sympathectomy as recommended by Parsons and Norton.[4]

Summary

The case reported illustrates the development of lysis and absorption of the metatarsal and phalangeal bones in the right foot of an obese female diabetic. These changes are believed to be secondary to a proved diabetic neuropathy, and are comparable to those occurring in other diseases producing neuropathic joint lesions. We were especially impressed by the absence of infection, the freedom from pain, the presence of findings indicative of diabetic neuropathy and retinopathy, and the integrity of the circulation of the involved foot.

Acknowledgment

The author is indebted to Dr. W. K. Kalbfleisch, of the Department of Roentgenology of the Wheeling Clinic, and to Dr. A. K. Butler, of the Department of Roentgenology of the Ohio Valley General Hospital, Wheeling, West Virginia, for interpretation of the roentgenograms.

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XANTHOMA DIABETICORUM *

By Esar Gordon Margolin, 1st Lieutenant, MC, *Omaha, Nebraska*

In recent years cholesterol and its esters have been singled out of the lipid constituents of the body for special consideration, largely because of their relationship to atheromatous changes and partly because of their chemical similarities to adrenal and sexual hormones. Clinicians have been impressed with the importance of the cholesterol levels in certain disease states, and the measurement of cholesterol is now a standard test in most clinical laboratories. A recent case of xanthoma diabeticorum, manifesting striking alterations in cholesterol metabolism occurring in the course of uncontrolled diabetes mellitus, is presented.

Case Report

Present Illness: A 21 year old white soldier had been in Korea for two months when he was evacuated to the 382d General Hospital on December 17, 1951. Approximately three weeks prior to this admission a "rash" first appeared about his elbows and rapidly spread to involve his buttocks and posterior thighs. When he reported to sick call on December 10, two weeks after development of these skin lesions, sugar was noted in his urine. For the following week he was observed and treated at the 25th Evacuation Hospital, Korea. This installation reported that on admission the patient's urine contained sugar (4 plus), acetone (2 plus) and diacetic acid. Blood sugar was 381 mg. per cent and carbon dioxide combining power was 41.0 vol. per cent. The vessels in his fundi appeared white and his blood grossly had a lavendar color. Initial cholesterol level was 1525 mg. per cent. The patient was treated with rigorous insulin therapy, fluids and a starvation-low fat diet.

Further questioning revealed that in a three month period during the spring of 1951 the patient had lost 17 pounds for no apparent reason, but had maintained his weight at this lower level since. There was some slight increase in his appetite starting around June, 1951. Polyuria and polydipsia were never very prominent. In October he had fallen and abraded his left leg, right knee and right forearm. The lesion on the knee healed without difficulty but the other two had never healed. For several weeks he had noted distinct fatigability and some generalized weakness.

The patient's maternal grandmother was the only member of the family known to have had diabetes.

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From the Medical Service, 382d General Hospital, APO 54, c/o PM, San Francisco. Present address: 116 So. 50 St., Omaha.

FIG. 1. Xanthoma diabeticorum before treatment.

Physical Examination: Temperature, pulse and respirations were normal; blood pressure was 110/70 mm. of Hg. The patient was a well developed white male in no distress. There was a generalized waxy appearance of the skin, though the color of the mucosal surfaces and the nailbeds was fair. Hair distribution was normal. No acetone odor was detected on the breath. The neck was not rigid, the trachea was found to be in the midline, and the thyroid gland was not palpably enlarged. The eyes were totally normal to inspection, there being no icterus, arcus or corneal deposits. On examination of the fundi at this time there was no evidence of the reported change in color of the vessels; the eyegrounds were normal in all respects. The nasal septum was somewhat deviated to the left. There was some mucopurulent discharge on the posterior pharyngeal wall. The lungs were clear throughout except for intermittent harsh breath sounds at the left base laterally. The heart was not enlarged to percussion, the apical impulse being found in the fourth intercostal space within the midclavicular line; the rhythm was regular and the tones were loud and clear. A very faint systolic blowing murmur was heard at the apex only when the patient was supine. The second sounds in the aortic and pulmonic areas were equal. The peripheral pulses were of poor volume, all being palpable, including the dorsalis pedis and posterior tibial pulses bilaterally. In the abdomen the liver was palpated 1 cm. below the right costal margin; its edge was smooth and it was not tender. The spleen and kidneys could not be felt. Neurologic examination revealed that the deep tendon reflexes were all present but hypoactive in response, and that the vibratory perception was intact.

There were numerous discrete whitish to yellowish nodules, varying in size up to 3 mm. in diameter, scattered about most of the skin surfaces, but distinctly most numerous on the buttocks, posterior thighs and dorsal surfaces of the upper extremities. They were also found sparsely on the cheeks, back, ventral surfaces of the extremities and on the scrotum. These lesions were hard, nontender and deeply set into the skin; some had umbilicated surfaces and a few were topped with thin crusts. There was no inflammation of the surrounding skin. In addition, the patient was noted to have two old unhealed abrasions containing considerable amounts of granulation tissue, localized just below the right elbow and over the left lateral

tibial condyle. Numerous confluent nodular lesions, similar to those described above, were present within these masses of granulation tissue.

Laboratory Data: Blood count: hemoglobin, 12.4 gm.; hematocrit, 35 per cent; leukocytes, 4,100 per cubic millimeter, with normal differential count. Corrected sedimentation rate, 8 mm./hr. The urinalysis performed on admission revealed 4 plus sugar and no acetone. Repeated urinalyses revealed maximal random concentration to be 1.018, protein negative and microscopic negative. Intermittent glycosuria was dependent upon the degree of diabetic control. Total eosinophil count on December 27 was 255 cells/cu. mm. Blood sugar level on admission was 284 mg. per cent. Thereafter, readings varied from a high of 361 to a low of 74 mg. per cent. Carbon dioxide combining power was 59.8 vol. per cent on admission. Nonprotein nitrogen was 38 mg. per cent; total protein, 6.0 gm. per cent, with the albumin fraction of 3.8 and the globulin of 2.2 gm. per cent; alkaline phosphatase, 6.7 Bodansky units; van den Bergh: direct, 0.09, and indirect, 0.28 mg. per cent; cephalin flocculation, negative. Cardiolipin microflocculation test was negative.

Serum cholesterol level on admission was 668 mg. per cent, just one week after having been reported at 1525 mg. per cent by the previous installation. Esters at this time were 429 mg. per cent representing 64 per cent of the total figure. Successive weekly cholesterol values were 458, 442, 298 and 249 mg. per cent. With this last determination, the esters were 181 mg. per cent (72 per cent) (table 1).

TABLE I

Date	Cholesterol mg.%	Chol. Esters mg.%	Blood Sugar mg.%	CO_2 C. P. vol.%
December 10	1525*		381*	41.0*
17	668	429	284	59.8
24	458		156	
31	442		361	
January 8	298		118	
15	249	181		

* Reported by 25th Evacuation Hospital.

X-ray studies of the chest, the pelvis and thighs and the skull were all within normal limits.

An electrocardiogram taken December 18 was entirely normal.

Course in Hospital: Though the patient was symptom-free on admission, during his five weeks' hospitalization he did note progressive increase in his strength and vigor. His waxy pallor did not completely disappear, despite the fact that his hemoglobin rose from 12.4 to 15 gm. on ferrous sulfate medication. His weight was stable at 155 pounds in this interval.

The patient's diabetes was easily controlled by dietary and insulin therapy. Protamine zinc insulin, 40 units daily, was started soon after admission and was supplemented with premeal injections of regular insulin, dependent upon his urinary findings. Several readjustments were made in this schedule as observation progressed: he first required 55U of protamine zinc insulin with 20 units of regular insulin in separate injections each morning; then adequate control was achieved by discontinuing the regular; finally, at the time of discharge, he was aglycosuric on 40 units of protamine zinc insulin once daily. In the course of these adjustments the patient reported several very mild attacks suggestive of hypoglycemia.

His diet was kept at a very low fat and low calorie level in an attempt to reduce his blood cholesterol level. The initial dietary prescription was carbohydrate 270

gm., protein 60 gm., and fat 30 gm., the total caloric content being 1,590. After the cholesterol level had fallen to 249 mg. per cent his diet was changed to C250, P80, F50.

On this régime there was gradual regression of the lesions of the skin. The papules on his face completely resolved and all others became softer, smaller and less colored. A biopsy of several of the lesions was performed on December 21. Microscopic examination revealed: "Nests of xanthoma cells are present in the corium. Evidence of cholesterol crystals in the tissue spaces is present as needle-shaped spaces. A few Touton giant cells are present." Chemical analysis of this tissue disclosed about 1 per cent cholesterol content.

Of incidental interest were two basal metabolic studies performed on this patient. On December 26 the reading was minus 25 per cent and on January 11 it was minus 30 per cent. The relationship of this finding to the hypercholesteremia is obscure.

Discussion

Since 1851, when Addison and Gull [1] reported the first case of eruptive xanthomata in a patient with diabetes mellitus, numerous other such case reports have appeared. In 1933 McGavack and Shepardson [2] collected 97 cases of this disease from the literature. Out of some 21,000 cases of diabetes seen by Joslin,[3] only 14 were complicated with xanthoma diabeticorum. At Oliver General Hospital, where there were 12,000 admissions in a three year period, Colonel Charles L. Leedham (personal communication) saw only one case of this disease. This syndrome constitutes a relatively rare complication of diabetes.

Xanthoma diabeticorum is an acute eruptive disease occurring in the course of severe diabetes. The lesions of the skin appear rather suddenly as discrete nodules, 1 to 3 mm. in diameter. They occur mostly on the extensor surfaces, including the elbows, knees, buttocks and back, but may also appear on the forearms, dorsa of the hands, toes, neck and face. Each lesion is hard and nontender, having a yellowish center and often bordered by a narrow zone of inflammation. Sometimes they are mildly pruritic. There is some tendency for these lesions to coalesce to form plaques, and occasionally there are fine telangiectatic vascular formations on their surfaces. There is sometimes carotenosis of the palms. The liver and the spleen may be enlarged.

Emphasis has been placed on the fact that these xanthomatous lesions localize on extensor surfaces,[4] the exact reason for such distribution being a matter of conjecture. Major [5] believes that trauma on extensor surfaces is an important predisposing factor.

This manifestation of diabetes is probably more common in men than in women,[6, 7, 8] occurring at any age and from one to 21 years (average, five years)[3] after known onset of the diabetes. Joslin,[3] in analysis of his 14 patients, reports an average blood sugar of 280 mg. per cent (range of 120 to 370 mg. per cent), and an average cholesterol level of 756 mg. per cent (range of 214 to 1600 mg. per cent) when this disease is first recognized. Not only is the serum cholesterol elevated but also all the lipid constituents of the blood are increased. The plasma has a characteristic milky appearance, attributed to the excess neutral fat which is present,[8] since high cholesterol levels alone do not produce such turbidity. Some observers [9] believe that a relative decrease in the amount of phospholipids, the third lipid substance of the body, is responsible for the milky appearance. These substances act as emulsifiers of the neutral fat and, if present in insufficient amount, allow the small fat particles to conglomerate to visible size.

The elevation of the total fat may be extreme, one case quoted by Thannhauser [8] being 22,000 mg. per cent, compared to normal levels of 400 to 700 mg. per cent. The blood in these cases is variously described as chocolate, violaceous and milky. Associated with hyperlipemia there is a notable change in appearance of the retinal vessels, which may appear light pink, salmon, waxy or entirely white in color [10]; this condition is known as lipemia retinalis, and is said to occur only when the total lipid level in the blood rises above 3500 mg. per cent.[11, 12]

When carbohydrate is not properly utilized in the liver of the diabetic, fat is then transported to this organ and accumulated therein for combustion. Hyperlipemia is thus a manifestation of excessive fat transportation.[8] Application of insulin in this situation, both to man and to experimental animals, permits proper utilization of the carbohydrates and a decrease in the demand for fatty substances; hence the hyperlipemia is readily diminished. There is no definite relationship between the height of the blood sugar and the level of neutral fat or cholesterol in the blood, nor is there any correlation between the degree of acidosis and the level of the lipid substances.[8, 12] For the most part, however, good control of the diabetic state by both diet and insulin will result in normal levels of circulating lipids. Thus, it is only in uncontrolled diabetic states, not necessarily related to acidosis or hyperglycemia, that the blood fat levels are found at abnormally high values.

Histologically, the eruptive xanthomata occurring secondary to hyperlipemia show only a few scattered foam cells in the midst of large amounts of inflammatory tissue.[14] Cholesterol crystals are frequently recognized in the extracellular spaces of these lesions. Touton giant cells are scarce to absent. This histologic picture is in contrast to that seen in either xanthomata associated with hypercholesteremia without hyperlipemia, or in xanthomata associated with normal serum cholesterol levels. In both of these conditions foam cells are abundant and inflammatory response is minimal. Thannhauser [8] believes that in these two instances the formation of the xanthomata is dependent upon altered cholesterol metabolism within the individual cells. In the situation under consideration, on the other hand, the lesions are probably due to phagocytosis of the excessive fatty substances by cells of the reticuloendothelial system. It should be noted that, if such be the case, the greater portion of the lesions so formed is due to the inflammatory response of the surrounding tissue and not to the actual accumulation of lipids. This fact is partially borne out by the chemical examination of the tissue removed in this case, revealing a content of cholesterol of only 1 per cent. Normal tissue levels of this substance are 0.15 to 0.3 per cent.[8] It is difficult to reconcile these observations with the clinical fact that these inflammatory nodules erupt rather suddenly, especially when hyperlipemic conditions have probably existed for some time.

Similar eruptive xanthomata also occur in hyperlipemia from other causes, such as chronic pancreatitis and myxedema, and can be distinguished from that due to diabetes by the normal glucose tolerance in these syndromes. There is also a form of idiopathic hyperlipemia, sometimes associated with glycosuria, in which eruptive xanthomata appear; this disease is cured by a diet low in fat and does not require the addition of insulin.[8] The lesions of xanthoma tuberosum are usually of larger size, generally assuming the configuration of plaques, and are associated with hypercholesteremia not accompanied by increased levels of

neutral fat or milky serum. In molluscum contagiosum the papules are umbilicated and their contents can be squeezed out through the tiny orifices on their surface.[1]

Current authors [2, 6, 15, 16, 17] agree on the form of treatment of this disease. A low fat diet, often low in total calories as well, along with insulin is required both to control the diabetic state and to reduce the hyperlipemia. In most instances the blood fat levels can be restored to normal. There is gradual, but complete, disappearance of the cutaneous nodules under this therapy. The lesions regress without scar formation in two or more months. No particular effect on the hyperlipemic state has been shown by the use of any of the lipotropic substances, including lipocaic, choline, lecithin and vitamin E.[18] The use of thyroid extract is considered inadvisable because no deficiency in this hormone is apparent. Adequate control on usual diabetic management régimes is obtainable but recurrences may appear with subsequent lapses in treatment. In those cases where carotenemia and hepatic or splenic enlargement are noted there is also gradual disappearance of these manifestations along with the general improvement.

Summary

1. A case is presented of uncontrolled diabetes manifesting a serum cholesterol of 1525 mg. per cent, xanthoma diabeticorum and lipemia retinalis.

2. The relationships of hypercholesteremia and hyperlipemia (excessive neutral fat) as well as acidosis and hyperglycemia to this disease are discussed.

3. Treatment, consisting of careful diabetic management with a low fat diet and adequate insulin, can be successful in restoration of blood lipids to normal and in causing the recession of the skin lesions.

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EFFECTIVENESS OF N-ALLYLNORMORPHINE IN THE MANAGEMENT OF ACUTE MORPHINE POISONING*

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The clinician of yesterday regarded morphine as the most valuable drug of his entire therapeutic armamentarium. Although it has been relegated to a less exalted spot and forced to share its value as a pain reliever by the newer synthetic narcotics, such as meperidine and methadone, it remains a highly useful and often employed medication. Hence the advent of an effective antidote, N-allylnormorphine (Nalline) is of signal importance. All physicians should become familiar with the pharmacology, dosage and method of employment of such a preparation, and it should be made readily available in all antidote kits and wherever morphine and its derivatives and allied synthetics are utilized.

Acute morphine poisoning may result from errors in calculation of dosage, untoward reactions to the average dose, or attempts at self destruction. Too often this drug is used for its sedative effects, as in its routine employment as a preanesthetic agent, or in allaying the restlessness associated with hemorrhage and shock. Such use is difficult to justify for, according to Beecher,[1] the patient pays too high a price for the relief obtained by the means of this agent, and the desired effect can be achieved better in other ways.

Average doses of morphine are contraindicated in certain circumstances, e.g., cases of acute and chronic liver disease, bronchial asthma, primary hypothyroidism, pituitary myxedema, adrenal insufficiency, kyphoscoliosis, chronic cor pulmonale, chronic pulmonary emphysema, head injuries, acute alcoholism, delirium tremens and convulsive disorders; and they are to be used with caution in debilitated states and in cases of gastrointestinal hemorrhage, shock and cerebral arteriosclerosis, and in infants and aged patients.[2]

As a rule, the toxic dose of the alkaloid for a normal adult who is not in pain is about 60 mg. Serious symptoms nearly always follow the ingestion of 100 mg., and doses of 250 mg. usually cause death.[3] The severity of the depression of vital functions due to opiate poisoning can be indicated by the lowering of the eosinophil count, which probably reflects activation of the adrenal cortex

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in response to anoxia. In cases in which the depression is not excessive, supportive therapy and mild stimulants such as caffeine or ephedrine have proved adequate. In more heavily narcotized individuals, the results of treatment, until recently, have not been altogether satisfactory. Death usually results from asphyxia.

Following is a report of a gratifying experience with Nalline in neutralizing the narcotic effects of an inadvertent overdose of morphine.

Case Report

A 56 year old white male veteran was admitted to the U. S. Naval Hospital in Philadelphia on July 17, 1952, complaining of abdominal pain, vomiting of three days' duration, and recent episodes of hematemesis. Since 1918 he had had numerous previous admissions to this and other hospitals for symptoms of peptic ulcer and alcoholic gastritis. The history revealed that he had had a gastroenterostomy, resection of a marginal ulcer, and a subtotal gastric resection with a gastrojejunostomy and splenectomy.

Upon admission he appeared to be in acute distress. The blood pressure was 130/90 mm. of Hg; pulse, 78; temperature 99° F.; weight, 156 pounds. There was an odor of alcohol on his breath. Except for a slightly injected pharynx and edentia, examination of the head and neck was negative. There were no clinical abnormalities of his heart or lungs. The abdomen was scaphoid and covered with several well healed scars. There was tenderness and muscle guarding in the epigastrium. Peristalsis was active. There were no spasm, palpable organs, masses or herniae. The prostate was enlarged about one and one-half times its normal size and was smooth and nontender. There was no evidence of gross blood or melena on digital rectal examination.

The pain did not seem to ease at first despite intravenous fluids or meperidine. Gastric aspirations, however, afforded relief. Routine studies revealed negative urinalysis, blood count and serologic test for syphilis. Liver profile studies showed a 3 plus cephalin flocculation and negative thymol turbidity; the serum bilirubin was 0.5 mg. per 100 ml.

During the patient's hospital stay it was noticed that he had a nonproductive cough which he claimed he had had for years. Hemoptysis was denied. His voice became progressively hoarse, and he stated that eight years before a tumor had been removed from one of his vocal cords. A chest x-ray revealed a focal area of cloudy density in the left apex and infraclavicular area which was interpreted as a granulomatous process. This had been noted on films taken on previous admissions. Several sputum and gastric smears and cultures were negative for acid-fast bacilli. Sputum smear was reported as showing *Micrococcus pyogenes*, alpha hemolytic streptococcus and *Staphylococcus albus*.

The patient was scheduled for bronchoscopy on July 31. At 8:45 a.m. the prebronchoscopy medications for five patients were given inadvertently to this patient. He received 40 mg. of morphine sulfate and 2 mg. of scopolamine. The mistake was soon discovered. At 9:15 a.m. the patient was sleeping very soundly, and his pulse was slow and strong. The corneal reflex was absent, the pupils were miotic and there was a depression of all his deep tendon reflexes. Respirations were depressed to eight per minute. The blood pressure was 106/62 mm. of Hg.

At 9:20 a.m., 10 mg. of N-allylnormorphine were administered intramuscularly. By 10 a.m. his respiratory rate had increased to 18 per minute, and a corneal reflex could be elicited. Deep tendon reflexes were active and the patient could be aroused easily. His speech was slurred and incoherent, and he fell off to sleep immediately

when not stimulated. At 10:50 a.m. he was given one-half of a cup of black coffee, and by 11:45 a.m. he was up and around, feeling well and eating his lunch unconcernedly. His blood pressure and respiratory rate remained constant after 10:00 a.m. The patient did not demonstrate any effects from this morphine poisoning during the rest of his hospital course, which ended on August 28.

Discussion

Normorphine and norcodeine (the prefix "nor" refers to the demethylated compound) were prepared by von Braun [4] in 1914. Demethylation of morphine, codeine and other related alkaloids diminishes their analgesic properties. Pohl found that N-allylnorcodeine stimulated respiration and antagonized the depressing action of morphine on the respiration. Since morphine is a stronger narcotic than codeine, the synthesis of N-allylnormorphine (hereafter designated Nalline) was undertaken with the hope that it might retain the analgesic and narcotic potency of morphine but lack the respiratory action. McCawley, Hart and Marsh [5] and Hart [6] found that Nalline had a stronger antagonistic action on the depression of respiration evoked by morphine than did N-allylnorcodeine.

In studying the antagonistic effects of Nalline on morphine, Unna [7] found that in dogs, Nalline rendered subsequent injections of morphine entirely ineffective when injected within one hour, and markedly attenuated the effects of morphine when given two to three hours afterwards. Dogs initially intoxicated with morphine regained normal behavior within 15 minutes after Nalline was exhibited. In mice the toxicity of Nalline is about the same as that of morphine; however, Nalline made the animals more resistant to the toxic effects of morphine. Nalline is much less effective than morphine in raising the threshold for pain in mice. It does not show any effects in influencing the manifestations of the apomorphine intoxication in rabbits or dogs.

Hart and McCawley [8] demonstrated in animal experiments that the replacement of the N-methyl group of morphine by N-allyl eliminates the respiratory depressant action, does not diminish the analgesic action, and alters the action on the intestinal tract and the central nervous system excitant action in the cat. They concluded that in most respects the N-allyl derivative is antagonistic to the parent compound.

Smith, Lehman and Gilfillan [9] studied the analgesic potency of Nalline and the antagonism between Nalline and several analgesics. They concluded that Nalline had a weak analgesic action in rats; in dogs, doses of 2 to 30 mg. per kilogram had no effect on pain threshold; but when Nalline was injected one hour after the administration of small active doses of morphine, methadone, hepazone, acetyl-dl-methadol or isonipecaine, the pain thresholds returned to control levels in from five to 10 minutes. Similar results were obtained in from one to three minutes when the antagonists were given intravenously. Huggins, Glass and Bryan [10] produced experimental evidence to show that Nalline was antagonistic to the respiratory depression caused by codeine, dihydromorphinone (Dilaudid), meperidine (Demerol), methyldihydromorphinone (Metapon) and methadone in dogs.

Since the site of action of morphine is generally assumed to be central, it would appear that Nalline, by virtue of its chemical similarity to morphine, exerts its actions upon the same centers as morphine, rendering them less sensitive to

morphine by chemical antagonism and displacement from the cell. This is an example of a relatively new principle of therapeutics, the concept of competitive antagonism of structurally related compounds. The analogues are believed to be effective because of competition for attachment to specific cell receptors. The antagonisms between sulfanilamide and para-aminobenzoic acid, aminopterin and folic acid, vitamin K and Dicumarol, histamine and antihistaminic drugs, penicillin and glutathione, ascorbic acid and glucose-ascorbic acid, pyridoxine and desoxypyridoxine, as well as several other important drug groups, are other examples of this phenomenon. Although most of the studies in this field during recent years have been concerned with the antagonism of essential metabolites by a variety of their structural analogues, the principle has already been extended to include materials other than essential metabolites, such as the opiates.

The effects of Nalline in normal non-narcotized human volunteers were investigated by Eckenhoff, Elder and King.[11] They found that in doses of 5 to 10 mg., given intravenously, the respiratory rate was not markedly affected; the respiratory minute volume was diminished on an average of 35 per cent, which reached its peak in from five to 10 minutes, and lasted for 40 minutes; the pulse rate and blood pressure were usually unchanged, and all subjects complained of a tired feeling and exhibited a pallor similar to that frequently seen after intravenous morphine. They also revealed that Nalline was effective against large doses of morphine sulfate or Demerol, but was ineffective in counteracting the depression caused by cyclopropane, ethyl ether or thiopental.[12] In patients given 20 to 90 mg. of morphine sulfate, or 200 to 600 mg. of Demerol, intravenous administration of 5 to 10 mg. of Nalline doubled or tripled the respiratory rate and increased the respiratory minute volume as much as 250 per cent within 1 to 2 minutes. These peaks declined gradually, but remained above depressed levels for a 60 minute period. There was an elevation of blood pressure in cases in which it had been depressed by the narcosis. In normotensives there was no effect on the blood pressure, except in some cases in which larger doses were used.

In the usual doses, Nalline has little awakening effect. The patient can be aroused but soon goes back to sleep. This was observed in our case and several other reported cases. In humans Nalline slows the heart rate, whereas in animals a tachycardia usually follows its administration. It has been shown that, when injected prior to an opiate, Nalline inhibits the respiratory and circulatory depression caused by the opiate, whereas when injected into a narcotized individual it stimulates the depressed respiration, but appears not to counteract the sedative effect produced by the narcotic.[13]

In 255 obstetrical patients, Nalline significantly shortened the interval between the delivery of the chin and the infant's first gasp, or the establishment of respiration when the child was born of a mother in a moderate or deep state of depression caused by analgesics and sedatives.

Nalline given to addicted persons has precipitated signs of withdrawal within 15 minutes of administration. It is conceivable that Nalline can be used to diagnose suspected addicts. However, until those engaged in such a specialized study have fully reported their experiences, it is not recommended that this drug be so employed at this time.

The average effective dose of Nalline is 10 mg., administered intravenously,

intramuscularly or subcutaneously. It may be repeated in 10 to 15 minutes. In their investigations, Eckenhoff, Elder and King, *loc. cit.*, found that second injections were less effective than the first, and that third injections were often ineffective. In cases of severe respiratory depression, total doses as high as 40 mg. have been given. The optimal dose is not known as yet. No serious toxic effects have been noted following its use, but Wikler [14] reported that high dosages given to volunteers produced dysphoria, miosis, pseudoptosis, lethargy, mild drowsiness and sweating. Occasionally there occur nausea, heaviness in the limbs, and hot and cold flashes. The lethal dose for a man is not yet known.

Nalline was used successfully in four cases of opiate poisoning by Eckenhoff, Hoffman and Dripps, *loc. cit.* Chase, Boyd and Andrews [15] report on its use in a 60 year old male who had signs of toxicity to Dilaudid and subsequently to Dromoran. Two cases of methadone poisoning were favorably influenced by this antagonist.[16]

Results to date have thus shown that this new drug, the first specific opiate antagonist, has many of the properties of an ideal analeptic, including a wide field of usefulness, effectiveness in small doses, sustained effectiveness for two to three hours, wide margin of safety, and failure to produce convulsions in average therapeutic doses.

Summary

1. Nalline is the first specific opiate antagonist synthesized for clinical use.

2. A case of morphine poisoning successfully treated with this drug is reported.

3. The pharmacology, physiologic properties and clinical uses of Nalline, based upon its successful competitive action against morphine and allied natural and synthetic derivatives, have been discussed.

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ACUTE HYPERTROPHIC OSTEO-ARTHROPATHY ASSOCIATED WITH SUBACUTE BACTERIAL ENDOCARDITIS *

By MALCOLM C. MCCORD, *Denver, Colorado,* and JOHN MOBERLY, *Dubuque, Iowa*

GENERALIZED hypertrophic osteo-arthropathy may cause a definite symptom complex entirely apart from, and often preceding, the symptoms arising from the primary disease. This symptomatic state was clearly described in the initial reports of this interesting disease process. The patient presented by Bamberger in 1889 [1] and, with additions, in 1891,[2] and the patients described by Marie in 1890,[3] evidenced arthritis and deforming skeletal changes. The term applied by Marie to this lesion, "osteo-arthropathie hypertrophiante pneumique," in itself indicates the emphasis placed on the bone and joint manifestations with enlargement of the extremities. The early reports by the English physicians Thorburn,[4] Godlee [5] and Springlethorpe [6] also detailed the symptomatic pattern of these bone and joint manifestations.

Until fairly recently the symptoms associated with hypertrophic osteo-arthropathy have received little attention. However, a renewed interest in these bone and joint manifestations has arisen from studies of patients with intrathoracic neoplasms. Thus, Craig,[7] Van Hazel,[8] Temple,[9] Berg [10] and Pattison [11] have again described the presence of arthritis, pain in the long bones and swelling of the extremities in patients with hypertrophic osteo-arthropathy. These authors have emphasized the importance of recognition of these symptoms in establishing an early diagnosis of neoplasms of the chest.

The presence of symptomatic osteo-arthropathy may also be of diagnostic

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importance in the diagnosis of subacute bacterial endocarditis. The following case report is presented to illustrate this fact.

Case Report

A 49 year old Negro man was first admitted to the medical service on February 20, 1950. Six months prior to admission the patient had noted the onset of exertional dyspnea, cough and orthopnea. These symptoms forced the patient to stop work at that time and progressed in severity until admission. During the week prior to hospitalization the patient coughed up blood-streaked sputum. Except for frequent and prolonged upper respiratory infections the patient had been in good health prior to the present illness.

The significant physical findings on this admission were limited to the cardiovascular system. The heart was enlarged to the left to the anterior axillary line by percussion. A systolic thrill was palpable at the cardiac apex. Auscultation at the apex revealed a loud snapping first heart sound, a grade IV blowing systolic murmur, and a soft, low pitched rumbling diastolic murmur with presystolic accentuation. A soft, high pitched, blowing diastolic murmur was audible along the left sternal border. The second heart sound in the left second intercostal space was increased in intensity and was reduplicated. The blood pressure was 110/70 mm. of Hg. Fluoroscopic examination demonstrated enlargement of the right and left ventricle and the left auricle. In the posteroanterior view four distinct arcs were present along the left cardiac border. Following digitalization and reduction of sodium intake the patient lost 11 pounds in weight and was discharged on March 15, 1950. The diagnosis was rheumatic heart disease with mitral stenosis and insufficiency and pulmonic insufficiency.

One month following discharge the patient experienced the onset of aching pain in the finger tips and toes. This pain increased in severity and extended up the extremities to the elbows and knees. The pain was constant in character, was not related to motion, was aggravated by pressure and was of such severity as to prohibit walking and prevent sleep. During this period fever was present, with afternoon levels varying from 100° to 102° F.

The patient was admitted to the medical service for the second time on May 5, 1950. Examination at this time revealed the same cardiac findings as on the previous admission. The finger tips were bulbously enlarged, markedly tender, and soft at the nail beds. The nails themselves were not significantly curved. There was tenderness to palpation along the bones of the forearm. The toes demonstrated an appearance similar to the fingers but to a lesser extent. Slight nonpitting edema was present over the ankles. Palpation along the anterior margins of the tibia caused marked pain.

Roentgen studies of the long bones shortly after admission revealed no abnormalities. Reëxamination on June 16 demonstrated extensive periosteal thickening along the shafts of the metacarpals, the radius, ulna, tibia and fibula bilaterally, as demonstrated in figure 1.

Laboratory studies revealed a white blood corpuscle level of 19,600; the hemoglobin was 7.5 gm. Blood cultures revealed a growth of micro-aerophilic *Streptococcus viridans* which was sensitive to penicillin. Penicillin therapy was begun on the ninth hospital day. After two days of therapy the patient noted marked diminution in the severity of the pain in the extremities. Positive blood cultures were obtained on May 17, June 11 and June 13. Aureomycin therapy was therefore initiated on June 13. On June 21 the patient died suddenly. Permission for postmortem examination was refused.

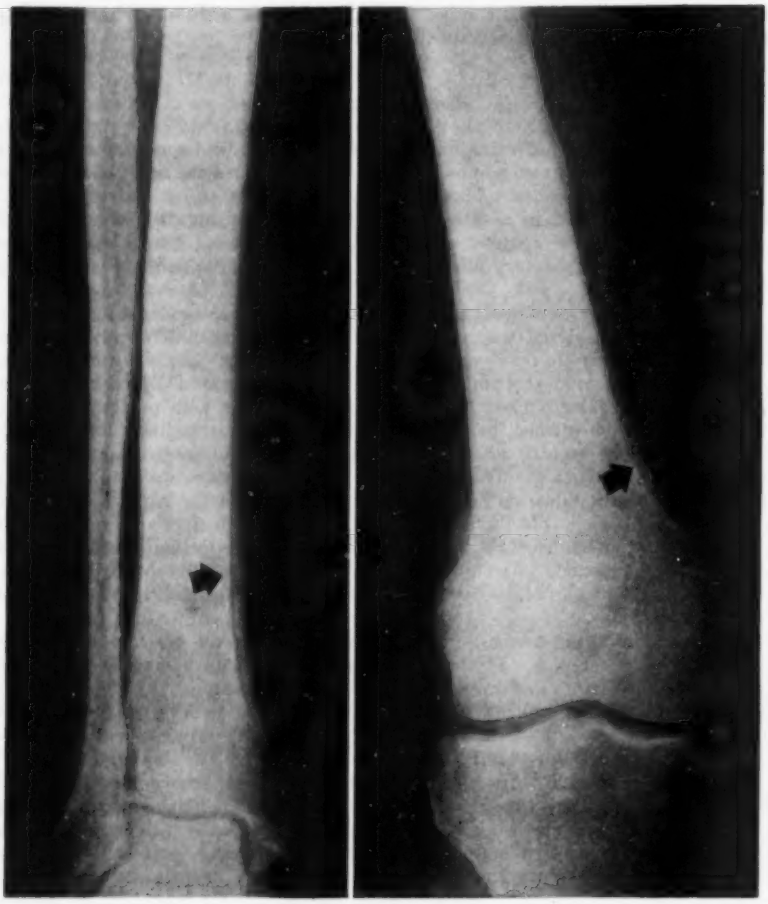

FIG. 1. The right tibia and fibula are shown on the left and the lower end of the right femur is shown on the right. Extensive periosteal proliferation is present along the shafts of these long bones, as indicated by the arrows.

DISCUSSION

Generalized hypertrophic osteo-arthropathy may be totally asymptomatic and be manifest clinically only by the presence of clubbing of the fingers and toes.[12] There may be symptoms of a chronic nature simulating rheumatoid arthritis.[18] Occasionally the symptoms may occur abruptly and with such severity as to be incapacitating in themselves. Descriptions of these acute and chronic symptoms have been presented in thorough reviews of this subject by Mendlowitz [14] and by Locke and Grollman.[15] The pathologic alterations in the bone, periosteum and synovia of patients with symptomatic hypertrophic osteo-arthropathy have been described by Gall and associates.[16]

Hypertrophic osteo-arthropathy rarely occurs with uncomplicated valvular heart disease [12, 14, 15] but is frequently present in association with subacute bacterial endocarditis.[17, 18] Pain occurring in the fingers of patients with subacute bacterial endocarditis as a result of hypertrophic osteo-arthropathy may be confused with the pain arising from Osler's lesions. The generalized distribution of pain and tenderness aids in differentiating hypertrophic osteo-arthropathy from the localized visible or palpable Osler's node. Joint pain resulting from hypertrophic osteo-arthropathy in patients with rheumatic heart disease and subacute bacterial endocarditis may be mistaken for rheumatic polyarthritis. A precise distinction in such instances rests on the demonstration of the characteristic periosteal proliferation on roentgenologic examination in hypertrophic osteo-arthropathy.

Conclusion

1. A patient with acute hypertrophic osteo-arthropathy associated with subacute bacterial endocarditis is presented.

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EDITORIAL

THE CHANGING PATTERN OF SYPHILIS 1941–1953

THE past 12 years have witnessed nearly incredible developments in the epidemiology, treatment, and laboratory diagnosis of syphilis, all of which are of major importance to the internist.

THE EPIDEMIOLOGY OF SYPHILIS

Accurate data as to the incidence and prevalence of syphilis are not available in the U. S. prior to 1941; and a breakdown by stage of disease (i.e., the number of fresh infections, thereby permitting an estimate of trend of incidence) first began to show some accuracy in 1943.

The numbers of cases reported to the Public Health Service among civilians in the Continental U. S. (excluding territories and military cases) are shown in condensed form in table 1. Only four years—1941, 1943, 1947, and 1952—are included, for the sake of brevity. In the four diagnostic categories listed, the figures in bold face type represent the peak years of discovery. From the original base line level of 1941, the discovery rate of early latent syphilis (i.e., infections definitely or presumably of four years or less in duration) and of late latent (more than four years in duration) and late symptomatic cases reached a peak in 1943, and has steadily declined since. The peak was due to the nation-wide application of mass blood testing, by law (as in premarital and prenatal examinations); by regulation

TABLE I

Cases of Syphilis in Civilians in Continental United States (Known Military Cases Excluded) Reported to the Public Health Service (Figures Given Are to Nearest 1000)*

	Total Syphilis	Primary and Secondary	Early Latent	Late Symptomatic and Latent	Congenital
1941	**486000**	68000	109000	203000	**18000**
1943	**576000**	82000	**149000**	**252000**	16000
1947	373000	**107000**	108000	122000	12000
1952	169000	12000	38000	102000	9000

* From V.D. Fact Sheet, Division of Venereal Disease, Office of Statistics, Federal Security Agency, Public Health Service, December 1952, Issue No. 9, p. 10.
The figures in bold face type represent the peak years of reporting of the four diagnostic categories included.

(as in the Armed Services); and by custom (as in routine examinations of ill persons by doctors, or of well persons in industry). The fall which in 1952 had reached a level only 40 per cent of the 1943 peak, is due in part only to the sharply decreased incidence of fresh infections, presently discussed. More largely it is a result of the beginning exhaustion of the reservoir of previously unidentified latent and late cases.

The peak of discovery of congenital syphilis,* 18,000 cases, was in 1941, with a progressive fall since, to a 1952 level one-half as great.

Fresh infections, on the other hand, starting at 68,000 in 1941, reached a near epidemic peak of 107,000 in 1947, and then began a precipitous drop to 12,000 in 1952, a decrease in incidence (from the peak) of nearly 90 per cent. This is the really important figure, which raises hope that the control of syphilis, if not its complete eradication, may actually be a not too distant available goal.

A decline in the incidence of fresh infections with syphilis in the U. S. and Western Europe has been under way for at least 100 years.[1] Punctuated by periodic peaks during years of particular population instability (especially wars, revolution, and their immediate aftermaths), this decline has followed nearly a straight line until 1948, since when it has become much more precipitous. Like the parallel 100 year decline in the morbidity and mortality of tuberculosis, it has proceeded almost without regard to the application of public health control measures, or (until penicillin) to the effectiveness of chemotherapy. The abrupt acceleration of the decline since 1948, however, is almost certainly due to the widespread use of effectively treponemicidal antibiotics, including aureomycin and terramycin as well as penicillin, not only for the treatment of syphilis itself but for many other diseases as well.

The internist will do well to remember, however, that despite the spectacular decline in the incidence of fresh infections, he is likely to encounter diagnostic and therapeutic problems of late syphilis for at least a generation to come.

The Treatment of Syphilis

Penicillin, first introduced into the treatment of syphilis in 1943, has now completely replaced arsenic, bismuth and mercury in all stages of syphilis. Treatment which only a decade ago required a disagreeable, dangerous, and expensive 18 months to five years to complete, may now be given safely, painlessly, and inexpensively in a few days or weeks. Early syphilis is readily curable (seronegative primary nearly 100 per cent, seropositive primary and early secondary about 85 per cent) with any regime of penicillin administration which provides a detectable serum level of 0.3 unit/c.c. or more for 7 to 10 days. With the new relatively insoluble and slowly absorbed preparations (e.g., N,N'-Dibenzylethylenediamine Dipenicillin G) a single injection of 2.4 million units is reported to be effective,[2] though most thera-

* This figure does not represent the number of infants with congenital syphilis born in the specified year; but instead the number of persons of any age first diagnosed as having congenital syphilis within that year.

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pists prefer a total of 6.0 million units of a repository penicillin given in 10 divided doses, daily, every other day, or twice weekly.

The repository preparations are apparently quite as effective (on an ambulatory basis) as aqueous penicillin "around the clock" in hospital.

Congenital syphilis can be completely prevented (almost no failure) by 6.0 million units penicillin given to the pregnant syphilitic mother at any period of pregnancy, but preferably before the seventh month.

Latent syphilis, early or late, is adequately treated with the same total dose as for early syphilis, as is also benign late (gummatous) syphilis. In cardiovascular and neurosyphilis, dosage ranges may be higher (10 to 20 or more million units) and the duration of treatment a little longer. Paradoxically, however, and judging by its effect on spinal fluid abnormalities, penicillin is even more successful in neurosyphilis of any type than in early syphilis.

Other antibiotics, especially aureomycin, terramycin, and erythromycin, have some antisyphilitic activity, but are not as effective as penicillin.

Some therapists still employ fever therapy (induced tertian malaria) in selected cases, especially primary optic atrophy, where the effectiveness of penicillin is not yet completely demonstrated; and in general paresis, where initiation of treatment with penicillin may cause serious, even disastrous, Herxheimer reactions.

The topical use of cortisone in inflammatory ocular lesions has completely revolutionized the outlook for interstitial keratitis, a remarkably resistant lesion of congenital syphilis.

The Serodiagnosis of Syphilis. The Phenomenon of Chronic Biologic False Positivity and Its Etiologic Background

Both from biologic and clinical points of view, the most interesting developments of the past five years relate to the phenomenon of biologic false positivity (BFP) in serologic tests for syphilis, its recognition by means of the treponemal immobilization (TPI) test, and its etiologic background.

It has long been known that reagin, the antibody which appears in the serum in quantity following treponemal infection (syphilis, yaws, and pinta), or a reagin-like substance also reacting with beef heart lipoid antigens, is present (a) in minute amount in the serum of most if not all normal persons; and (b) in increased quantity under the influence of a number of factors extraneous to syphilis. When persons in these two latter categories show positive results with standard serologic tests (excluding technical error), they are spoken of as BFP reactors.

It is pertinent to enquire here into what is meant by a "positive standard STS." * The sense in which the term is employed in this discussion is the same in which the practising physician employs it, i.e., *the presence of reagin*

* STS = serologic test for syphilis, limited in this discussion to standard serologic technics employing lipoid antigens.

in the patient's serum in any amount ranging from the merest trace (a "doubtful" result is indicative that the amount is in quantitative terms, less than 1 dilution unit) to high titer tests (32 or more dilution units); *and by any one or all of the serologic technics employed.* The frequency with which the BFP phenomenon is encountered by the practitioner is in large part, therefore, a function of the sensitivity (*not* specificity) of the technic employed by the laboratory. Various technics differ in sensitivity in the hands of the originating serologist; any one of these varies in sensitivity when performed in different laboratories, or even, to some extent, from day to day in the same laboratory.

The physician is entitled to suspect a BFP reaction in parallel with his suspicion of syphilis when a verified standard positive STS is routinely discovered in a person, sick or well, who gives no history of infection with syphilis *or of reasonable exposure to it,* and who shows no physical evidence of the disease. The suspicion is strengthened if:

1. Quantitative tests with standard technics are of low titer, i.e., 8 dilution units or less. This is a very rough rule of thumb, however, since some BFP reactions are high titer (32 to 256 or more units) and patients with syphilis may, at any stage of infection, have low titer tests.

2. Qualitative and/or quantitative results with a battery of standard serologic tests are discrepant, e.g. (example A) complement fixation (Wassermann) test positive, flocculation tests negative, or (example B) complement fixation negative, Kahn standard test positive 2 units, Eagle flocculation positive 4 units, cardiolipin flocculation test negative. Suspicion is especially aroused if the serum is positive with less sensitive (e.g., Kahn standard), negative with more sensitive (e.g., cardiolipin) technics.

3. A negative history of infection and denial of exposure is backed up by epidemiologic evidence, e.g., demonstrable virginity, negative epidemiologic survey of familial and sexual contacts.

4. There is a history of a known precipitating cause of the BFP phenomenon, especially in a person known previously to be seronegative.

Prior to 1949, identification of the BFP reactor was a tedious and uncertain procedure, requiring elaborate clinical survey and often long term follow up.[3]

In 1949, the situation was abruptly changed by the brilliant immunologic studies of Nelson and Mayer [4] who demonstrated a treponemal immobilizing antibody in the serum of animals and man infected with syphilis or other treponematoses, but not in that of normal persons or of those suffering from non-treponemal diseases. The discovery of this antibody and the proof that it is distinct from reagin, made possible at once the development of the treponemal immobilization (TPI) test.

[3] Moore, J. E., Eagle, H., and Mohr, C. F.: Biologic false positive serologic tests for syphilis. III. A suggested method of approach to their clinical study, J. A. M. A. **115**: 1602 (Nov. 9) 1940.

[4] Nelson, R. A., Jr., and Mayer, M. M.: Immobilization of *Treponema pallidum* in vitro by antibody produced in syphilitic infection, J. Exper. Med. **89**: 369, 1949.

The application of the TPI test to the differentiation of syphilis from biologic false positivity has been discussed by Mohr, Moore, Nelson, and Hill.[5] In a more recent communication, Moore and Mohr[6] discuss the non-specificity of standard (beef heart lipoid antigen) serologic tests for syphilis, and describe the behavior of reagin and of the TPI antibody in treated and untreated syphilitic infection in man. They also describe two types of BFP reactions: (1) acute, characterized by the facts that they occur during or shortly after a wide variety of unrelated nonsyphilitic infections, and that they disappear spontaneously within not more than six months after infection; (2) chronic, marked by the absence of readily identifiable precipitating factors, and by their persistence over months or years, perhaps even a lifetime.

Applying the TPI test to some 300 seropositive patients in whom the diagnosis lay between latent syphilis and the chronic BFP phenomenon, all of whom had been studied on the basis of the collateral evidence outlined in numbered paragraphs 1 to 4 above and the additional rigid clinical criteria laid down in their 1940 paper, Moore and Mohr[6, 7] found that about 45 per cent were BFP reactors and did not have syphilis.

Confirmation of this approximately identical incidence of BFP reactors in groups of routinely discovered seropositive persons (conforming roughly to the qualifications described above) has been provided by Nelson,[8] in a U. S. Navy study; Curtis, of the University of Michigan[9]; Miller and Hill, Columbia-Presbyterian Medical Center[10]; and Miller of the Department of Health, Ontario, Canada.[11] The latter's data are especially interesting. When all three of a battery of standard serologic tests (Kahn presumptive, Kolmer complement fixation, and Kline flocculation) were "strongly positive," 8 per cent of the positive reactors were TPI negative. When the Kahn presumptive was positive but the two latter tests were discrepant (one negative or doubtful, the other positive), 43 per cent were TPI negative, and therefore BFP reactors.

The use of the TPI test under appropriate conditions[6, 7] permits, therefore, an answer to the troubled patient's question "Do I have syphilis?" When this question can be answered in the negative, there remains another and perhaps even more important question: "Why does the patient have a

[5] Mohr, C. F., Moore, J. E., Nelson, R. A., Jr., and Hill, J. H.: Studies on the relationship of treponemal immobilizing antibody to probable biologic false positive serologic tests for syphilis, Am. J. Syph., Gonor. and Ven. Dis. **34**: 405, 1950.

[6] Moore, J. E., and Mohr, C. F.: Biologically false positive serologic tests for syphilis. Type, incidence and cause, J. A. M. A. **150**: 467 (Oct. 4) 1952.

[7] Moore, J. E., and Mohr, C. F.: The incidence and etiologic background of chronic biologic false positive reactions in serologic tests for syphilis: preliminary report, Ann. Int. Med. **37**: 1156 (Dec.) 1952.

[8] Nelson, R. A., Jr.: The treponemal immobilization test in the U. S. Navy, Am. J. Syph., Gonor. and Ven. Dis. **37**: 1, 1953.

[9] Curtis, A. C.: Personal communication.

[10] Miller, J. L., and Hill, J. H.: Personal communication.

[11] Miller, G. W.: The use of the TPI test in a syphilis control program, Am. J. Syph., Gonor. and Ven. Dis., in press.

false positive blood test?" Moore and Mohr have begun a systematic study of this problem. In a preliminary report published in the Annals of Internal Medicine [7] and covering the first 51 patients studied, five patients were found to have proved collagen vascular disease (disseminated lupus erythematosus in four, rheumatoid arthritis in one); and in 21 others, there were clinical disorders pointing toward this diagnosis (usually disseminated lupus) but without as yet definite proof. In all of these, plus 14 others who were as yet clinically normal, there were laboratory abnormalities pointing to a quantitative and/or qualitative alteration of gamma globulin (positive protein flocculation tests in the absence of apparent liver disease, elevated serum globulin, altered serum electrophoretic pattern, etc.); and with these, often associated hematologic disorders, especially mild to moderate anemia, hemorrhagic phenomena, etc. Only six of the 51 BFP reactors were normal except for the BFP reaction itself.

Moore and Mohr conclude that the chronic BFP phenomenon is far from innocuous, as has heretofore been thought; that it is often related to and may be the first evidence of serious underlying disease [12]; that collagen disease may be closely related to it; and that if these observations are borne out by further study, an opportunity may be provided better to define the early manifestations and natural history of the collagen disease group.

Unfortunately for the widespread practical application of this new knowledge, the TPI test is a technically complicated and difficult procedure, available in only a few laboratories in the U. S.,[13] and in none of them (except for U. S. Navy personnel) on a purely service basis. Efforts to develop a simplified technic for the demonstration of the specific treponemal antibody are under way in several laboratories.[14, 15, 16, 17] These hold great promise that within the next few years, there may be available for general use a serodiagnostic test entirely specific for the treponematoses. If and when this occurs, present day beef heart lipoid antigens will perhaps continue in use, if at all, not for detection of syphilis, but instead for the particular purpose of recognition of the chronic BFP reactor!

J. E. MOORE

[12] Haserick, J. R., and Long, R., have also reported (Ann. Int. Med. **37**: 559 (Sept.) 1952) on "Systemic lupus erythematosus preceded (by several years) by false positive serologic tests for syphilis: presentation of five cases."

[13] Listed in "Treponemal immobilization test." Queries and Minor Notes, J. A. M. A. **151**: 962 (March 14) 1953.

[14] Nelson, R. A., Jr.: Le test d'immobilization des tréponèmes et le phénomène de l'adherence—disparition dans la syphilis, Presse med. **60**: 1719, 1952.

[15] Cain, R. M.: The phenomenon of treponemal agglutinations for the serodiagnosis of syphilis, Canad. J. Pub. Health **44**: 61, 1953.

[16] Harding, T. H., and Hollander, D. H.: Studies on the agglutination of *Treponema pallidum* by immune sera, presented before the Symposium on Recent Advances in the Study of Venereal Disease, Washington, April 30, May 1, 1953.

[17] McLeod, C. P., and Magnuson, H. J.: Agglutination of *Treponema pallidum* in syphilitic serums, presented before the Symposium on Recent Advances in the Study of Venereal Disease, Washington, April 30–May 1, 1953.

REVIEWS

Human Factors in Air Transportation: Occupational Health and Safety. By Ross A. McFarland, Ph.D., Associate Professor of Industrial Hygiene, Harvard School of Public Health. 830 pages; 18.5 × 25.5 cm. McGraw-Hill Book Co., Inc., New York. 1953. Price, $13.00.

This large book is in effect a companion piece on human hygiene to the author's earlier volume on human engineering, *Human Factors in Air Transport Design.* The canvas which Dr. McFarland has chosen to fill is extraordinarily large, and he has filled it with a mass of data. The result stands as evidence of his industry and proves his introductory statement that "aviation medicine comprises a *group* of biological and medical sciences." To which one might add fairly engineering, management, and public relations. Because of the wide range of topics which has been covered with varying degrees of intensity this volume will serve as a guide to the areas which are of especial concern to aviation medicine in its broadest sense, and the bibliographies will be of help to anyone beginning to track down what is known or thought in many phases of the field. The weaknesses of the book disclose what this reviewer believes to be the sheer impossibility of one man ever writing a text of this scope in which large sections are based on information which is second-hand or worse. The dilemma presented is the choice between single authorship with its attendant consistency in style but inadequate critique, and multiple authorship with its resulting duplication and outright contradictions. This book displays defects resulting from Dr. McFarland's having impaled himself on the first horn of the dilemma, and this despite the coöperation of a number of distinguished consultants. The result is that in certain areas, at least in those with which this reviewer has some familiarity, the treatment is uneven: there are the usual number of misstatements, unavoidable in a work of this size, but more disturbing is the tone of dogmatism which is used occasionally to make unqualified recommendations in a problem which is still unsettled and moot. Despite these shortcomings there is a wealth of information on such topics as selection and training of flight personnel, maintenance of their health and efficiency; selection, placement and health of ground personnel, safety on ground and in flight, sanitation, passenger and service problems, and health and medical services in air transport. There is no other one source-book for so wide a range of topics in this field and for that reason Dr. McFarland has performed a most useful service.

Joseph L. Lilienthal, Jr.

Infectious Mononucleosis. Modern Medical Monographs 5. By Sidney Leibowitz, M.D., Associate Physician, Beth Israel Hospital, New York. 163 pages; 14 × 22.5 cm. Grune and Stratton, Inc., New York. 1953. Price, $4.75.

This monograph, one of the Modern Medical Monograph series, represents a well written summary of current knowledge concerning infectious mononucleosis. The material is based chiefly on the author's observations in 25 sporadic cases of infectious mononucleosis. In addition, when appropriate to the subject under discussion, or where the author's experience is small in a particular phase of the disease, a review of the literature is included. Instead of repeating many well documented facts, the author has placed emphasis on the more unusual manifestations of the disease and the difficulties of diagnosis.

The body of the monograph is divided into three large chapters devoted to the clinical, hematologic and serologic manifestations of infectious mononucleosis. The major chapters are supplemented by shorter sections which discuss the cardiac and

central nervous system manifestations of the disease, a well written summary of the important clinical features and a rather superfluous group of case protocols from the author's files. A very complete bibliography is appended and includes most of the world literature pertinent to the subject.

The present publication is the first attempt in English to summarize the known facts and fallacies about infectious mononucleosis since the work of Bernstein in 1940. As a summary, the monograph is of value to the reader with special interest in infectious mononucleosis.

J. B. W.

Hypersplenism and Surgery of the Spleen. By WILLIAM DAMESHEK, M.D., and C. STUART WELCH, M.D., Pratt Diagnostic Hospital, The New England Center Hospital and Tufts Medical School, Boston, Massachusetts. 84 pages; 23 × 30.5 cm. (loose-leaf). Grune and Stratton, Inc., New York. 1953. Price, $10.00.

This book, an extension of *The Spleen and Hypersplenism* by Dameshek and Estren (1948), presents a rather complete discussion of the current concepts of the anatomy, histology, physiology and pathology of the spleen.

The material is presented in outline form with numerous illustrations and charts which serve to simplify a difficult subject. The book is bound in loose-leaf style and the contents are actually a condensation of an American Medical Association exhibit presented by the authors in 1950. There are seven large sections which consider the spleen in health and disease, as well as some aspects of splenic surgery. In addition to a small but select bibliography of pertinent literature, a chapter of conclusions is included.

The stated purpose in publishing this work is an attempt to increase the recognition and understanding of splenic dysfunction and, in particular, hypersplenism. The senior author is a well known proponent of a hormonal theory for hypersplenism; however, he presents views other than his own in this discussion and gives some space to the sequestration theories of Doan and Wiseman.

The latter section of the book deals primarily with splenic surgery. Included are sections on indications for splenectomy, technics and results of splenectomy in various disorders, and a special portion devoted to portal hypertension and its relief by shunting procedures.

There is no question but that the material summarized in this volume is of great interest to all acquainted with the spleen and its disorders. However, the outline and graphic method of presentation may prove to be an oversimplification for some readers.

J. B. W.

Tumors of the Parathyroid Gland (Atlas of Tumor Pathology, Section IV, Fascicle 15). By BENJAMIN CASTELMAN, M.D., Acting Chief, Department of Pathology and Bacteriology, Massachusetts General Hospital. 74 pages; 20 × 26 cm. (paper-bound). Published by the Armed Forces Institute of Pathology under the Auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C. 1952. Price, 65 cents.

In this work, several objections that might be cited against atlases have been artfully overcome. This has been accomplished by a text which plainly correlates the depicted material with function and clinical manifestations. Important anatomical features of the parathyroid glands and sustaining allusions to embryology are presented, followed by an exposé of hyperplastic and neoplastic lesions classified according to their capacity to influence calcium metabolism. The structural changes that result from this influence are presented to complete related clinico-pathologic entities.

Significant chemical features are presented but not enlarged upon. The reader is directed through the bibliography to valuable sources for details of parathyroid dysfunction.

The fascicular form of this atlas permits a choice of atlas material. This is economical and particularly advantageous to the clinician who has a special interest within a specialty. This source affords him an opportunity to acquire informative, illustrative material which is exceptionally pleasing from a photographic standpoint.

Although an atlas usually finds its greatest use in the hands of a pathologist, this publication promises equal usefulness to the surgeon and internist.

D. L. R.

Histologie und mikroskopische Anatomie des Menschen. By W. BARGMANN. Georg Thieme, Stuttgart, Vol. I, 1948, 210 pages, 192 figures and one colored plate (price, DM 19.60); Vol. II, 1951, 563 pages and 412 partly colored figures; 18 × 26.5 cm. Price, DM 45.00.

With the publication of the second volume this unique and original text of histology is complete. The first volume is devoted to the structure of protoplasm, cells and tissues; in the second volume the finer structure of organs and organ systems is described. In order to present the subject in the form of a dynamic morphology, mechanical architecture and a functional concept are emphasized throughout the book, physical properties and ultrastructure are given a prominent place in the discussion of protoplasm and certain cell types, and the most recent results are adduced, obtained by a large variety of methods of investigation, such as histochemical and physical examination, vital staining, tissue culture, microdissection, dark field examination, electron microscopy, x-ray photography, examination under the polarizing microscope, etc. In elucidating the static architecture of tissues and organs, the arrangement of elastic fibers, reticulin fibers and smooth muscle fibers is given a prominent place. Beautiful illustrations show the frequent occurrence of arteriovenous anastomoses and demonstrate their functional significance. The author seems to accept the results of the most recent researches in the light of which the structure of the central nervous system is a neurencytium of nerve and glia cells, but states that this condition does not conflict with either the neuron concept or cell theory. For many organs the changes occurring in old age are described. Many of the chapters are introduced by brief historical considerations accompanied by excellent portraits of pioneer workers. An abundant bibliography (with full title of each publication) follows each chapter. The illustrations are beautifully executed. While the illustration material is very abundant, one misses sometimes a picture which would illustrate at high magnification the cells composing an organ; in some instances a more ample marginal description would be welcome.

E. U.

Problems of Infancy and Childhood: Transactions of the Sixth Conference, March 17 and 18, 1952, New York, N. Y. Edited by MILTON J. E. SENN, M.D., Sterling Professor of Pediatrics and Psychiatry, Yale University School of Medicine, New Haven, Conn. 160 pages; 15.5 × 23.5 cm. Sponsored by the Josiah Macy, Jr. Foundation, New York. 1953. Price, $2.50.

This small volume represents another in the now familiar series of conferences arranged and published by the Josiah Macy, Jr. Foundation. As with the rest, a few investigators present their data which are discussed by a large group of well known scientists from similar and allied fields. Of three scientific presentations, two of them came from the Child Study Center at Yale University and deal with the psychological aspects of the first year of life. These papers were "Emotional De-

velopment in the First Year of Life" by Sibylle Escalona and "Observation of Individual Tendencies in the First Year of Life" by Katherine M. Wolf. In addition Ann Stewart, of the University of Washington, presented a study entitled "Excessive Crying in Infants—A Family Disease," and Knut Kjellberg presented "A Brief Review of WHO Activities" in the area of infancy and child care.

This book is a very valuable contribution to the understanding of infants. The authors are to be congratulated on their facility in stating clear concepts in simple language. This is a rare feat these days, especially in the psychological sciences, and we should be grateful. The reviewer was able to get little value from reading the voluminous discussion. This use of the "multidisciplinary approach" adds little to the study discussed and serves mostly as a sounding board for individual hunches, which are usually not of very general interest. In spite of this, however, the studies presented are so useful that the book is well worth being read by anyone concerned with understanding infants.

H. W. N.

Physical Examination of the Surgical Patient. By J. Englebert Dunphy, M.D., F.A.C.S., and Thomas W. Botsford, M.D., F.A.C.S. 326 pages; 16 × 24 cm. W. B. Saunders Company, Philadelphia. 1953. Price, $7.50.

This volume of 326 pages is generously illustrated by excellent black and white drawings and diagrams. The authors have enlisted able specialists from the Harvard Medical School and elsewhere in its preparation. The subject matter is presented in a succinct, orderly, regional manner.

This book should prove invaluable to students and internes. The chapters on examination of injured patients particularly should be useful to house officers working in receiving or accident wards. The check list for physical examination of the surgical patient is worthy of consideration by students, internes and surgical practitioners alike.

The volume was designed "to focus attention on the methods and importance of eliciting physical signs in surgical conditions." It has done so in a concise, attractive and well illustrated way.

H. C. H.

BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Dermatologic Formulary, From the New York Skin and Cancer Unit, Service of Dermatology (Dr. Marion B. Sulzberger, Director)—Revised, 1953. By Frances Pascher, M.D., Editor. 150 pages; 19.5 × 13 cm. 1953. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $3.00.

Diphtheria and Pertussis Vaccination: Report of a Conference of Heads of Laboratories Producing Diphtheria and Pertussis Vaccines, Dubrovnik, Yugoslavia, 13–18 October 1952. World Health Organization Technical Report Series No. 61. 88 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 55 cents.

Diseases of the Liver, Gallbladder and Bile Ducts. 3d Ed. (in two volumes). By S. S. Lichtman, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, Cornell University Medical College, etc. 1357 pages; 24 × 15.5 cm. 1953. Lea & Febiger, Philadelphia. Price, $22.00.

Effective Inhalation Therapy. By EDWIN RAYNER LEVINE, M.D., Chairman of the Committee on Physiologic Therapy, American College of Chest Physicians, etc.; with the coöperation of ALVAN L. BARACH, M.D., Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, etc.; J. WINTHROP PEABODY, M.D., Professor of Diseases of the Respiratory System, Georgetown University Medical School, Washington, D. C.; and MAURICE S. SEGAL, M.D., Clinical Professor of Medicine, Tufts College Medical School, Boston, etc. 159 pages; 24 × 16 cm. 1953. National Cylinder Gas Company, Medical Division, Chicago. Price, $4.50.

Endocrinology in Clinical Practice. Edited by GILBERT S. GORDAN, M.D., Ph.D., Assistant Professor of Medicine, University of California School of Medicine, and H. LISSER, M.D., Clinical Professor of Medicine and Endocrinology, etc. 407 pages; 23.5 × 15.5 cm. 1953. The Year Book Publishers, Inc., Chicago. Price, $10.50.

Expert Committee on Bilharziasis: First Report. World Health Organization Technical Report Series No. 65. 45 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30 cents.

Expert Committee on Biological Standardization: Sixth Report. World Health Organization Technical Report Series No. 68. 28 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 20 cents.

Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel: Second Report. World Health Organization Technical Report Series No. 69. 28 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 20 cents.

Joint FAO/WHO Expert Committee on Brucellosis: Second Report. World Health Organization Technical Report Series No. 67. 36 pages; 24 × 16 cm. (paper-bound). 1953. Published jointly by FAO and WHO and issued also as FAO Agricultural Studies, No. 24; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 25 cents.

Long-Term Diabetes: The Clinical Picture in Diabetes Mellitus of 15–25 Years' Duration with a Follow-Up of a Regional Series of Cases. By KNUD LUNDBÆK, M.D., Copenhagen, Lecturer in Internal Medicine, Aarhus University Medical School; Ophthalmological Section in Collaboration with VIGGO A. JENSEN, M.D., Copenhagen, Professor of Ophthalmology, Aarhus University Medical School; translated from Danish by AXEL ANDERSEN. 198 pages; 25 × 17 cm. 1953. Ejnar Munksgaard, Copenhagen, and Lange, Maxwell & Springer, Ltd., London. Price, D. Cr. 32/–.

The Major Metabolic Fuels: Number 5 of a Series of Symposia Sponsored by the Biology Department, Brookhaven National Laboratory, September, 1952. 234 pages; 25.5 × 17.5 cm. 1953. Associated Universities, Inc., under contract with the United States Atomic Energy Commission. Available from the Office of Technical Services, Department of Commerce, Washington-25, D. C., at $1.35.

Mechanisms of Urologic Disease. By DAVID M. DAVIS, M.D., Professor of Urology Emeritus, Jefferson Medical College, etc. 156 pages; 22.5 × 14.5 cm. 1953. W. B. Saunders Company, Philadelphia. Price, $4.50.

Milk Pasteurization: Planning, Plant, Operation, and Control. World Health Organization Monograph Series No. 14. By H. D. KAY, C.B.E., Ph.D., D.Sc., F.R.S., Director, National Institute for Research in Dairying, Shinfield, Berkshire, England; J. R. CUTTELL, A.M.I. Mech.E., Engineer, A.P.V. Co., Ltd., London, England; H. S. HALL, B.Sc., Head, Dairy Engineering Department, National Institute for Research in Dairying, Shinfield, Berkshire, England; A. T. R. MATTICK, B.Sc., Ph.D., Deputy Director, National Institute for Research in Dairying, Shinfield, Berkshire, England; and A. ROWLANDS, B.Sc., M.S., Managing Director, Astell Laboratory Service Co., Ltd., London, England. 204 pages; 24 × 16 cm. (paper-bound). 1953. Published jointly by FAO and WHO and issued also as FAO Agricultural Studies No. 23; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $2.50.

Die Pankreopathien. By PROF. DR. H. A. HEINSEN. 125 pages; 25.5 × 16.5 cm. (paper-bound). 1953. Ferdinand Enke Verlag, Stuttgart. Price, Geheftet DM 14.50.

Pediatric Clinics of North America. Volume I, Number IA. A Symposium on Poliomyelitis 1953. An Analysis of Recent Advances and an Outline of Clinical Management, Prepared with the Editorial Assistance of The National Foundation for Infantile Paralysis. 62 pages; 22.5 × 15 cm. (paper-bound). 1953. W. B. Saunders Company, Philadelphia. Price, Subscription $15.00 per year.

Report of the Medical Research Council for the Year 1951–1952. Committee of Privy Council for Medical Research. Presented by the LORD PRESIDENT OF THE COUNCIL to Parliament by Command of Her Majesty, June, 1953. 241 pages; 24.5 × 15 cm. (paper-bound). 1953. Her Majesty's Stationery Office, London. Price, $1.50.

Stammhirn und innere Erkrankungen. By DR. HANS-WILFRID WEDLER. 335 pages; 26 × 17.5 cm. (paper-bound). 1953. Springer-Verlag, Berlin. Price, DM 69.–

Survey of Antimalarial Agents: Chemotherapy of Plasmodium gallinaceum *Infections; Toxicity; Correlation of Structure and Action. Public Health Monograph No. 9.* By G. ROBERT COATNEY, Ph.D., W. CLARK COOPER, M.D., NATHAN B. EDDY, M.D., and JOSEPH GREENBERG, Ph.D. 323 pages; 25.5 × 19.5 cm. (paper-bound). 1953. Federal Security Agency, Public Health Service, Washington, D. C. Price, $1.25. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington-25, D. C.

Toxic Hazards of Certain Pesticides to Man, Together with a Select Bibliography on the Toxicology of Pesticides in Man and Mammals. World Health Organization Monograph Series No. 16. By J. M. BARNES. 129 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $1.50.

Transactions of the 12th Conference on the Chemotherapy of Tuberculosis, Held on February 9 to 12, 1953, at the Fulton County Medical Society, Atlanta, Georgia. 430 pages; 26 × 20 cm. (paper-bound). 1953. Prepared and Edited by the Veterans Administration Area Office, Atlanta, Ga., and Central Office, Washington, D. C.

Die Wirbelsäulentuberkulose und ihre Differentialdiagnose. By DR. J. E. W. BROCHER. 272 pages; 29 × 20.5 cm. 1953. Georg Thieme Verlag, Stuttgart; agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 78.–

COLLEGE NEWS NOTES

New A.C.P. Life Members

The College is gratified to announce that Dr. Charles F. Little, F.A.C.P., Great Falls, Mont., and Dr. George C. Turnbull, F.A.C.P., Evanston, Ill., have recently become Life Members.

A.C.P. Committees and Regents to Meet

The Board of Regents of the College and its various Committees will meet at the College Headquarters in Philadelphia November 14–15, 1953.

The Committee on Credentials will meet November 13–14. Proposals of new candidates must be filed in the Executive Offices sixty days in advance of the meeting at which they are to be acted upon. The next succeeding meeting of the Committee on Credentials will be held February 27–28, 1954.

Thirty-Fifth Annual Session, A.C.P.

The Thirty-Fifth Annual Session of the College will convene at the Conrad Hilton Hotel, Chicago, Ill., April 5–9, 1954. Dr. LeRoy H. Sloan, President, 5800 Stony Island Ave., Chicago 37, Ill., is in charge of the program of Morning Symposia, General Sessions and the Convocation. Dr. Howard Wakefield, General Chairman, 122 S. Michigan Ave., Chicago 3, Ill., is in charge of arrangements and the programs of hospital clinics, TV clinics, panel discussions and other special features.

The 1953 Directory, A.C.P.

The Revised Directory of the American College of Physicians is at press and will be ready for distribution later in the autumn. It will be furnished free of charge to all Life Members. Other members who sent in prepublication orders will pay $5.00. The regular post-publication price is $6.00.

Gifts to the College Library

The College gratefully acknowledges the gift of an autographed copy of the following two books by the author, Dr. R. H. Kampmeier, F.A.C.P., of Vanderbilt University School of Medicine, Nashville, Tenn.:

Physical Examination in Health and Disease, F. A. Davis Co., 1952.
Essentials of Syphilology, J. B. Lippincott Company, 1944.

A.C.P. Regional Meetings

At the time of the annual meeting of the West Virginia State Medical Association, the American College of Physicians held its West Virginia Regional Meeting at White Sulphur Springs, July 24, under the Governorship of Dr. Paul H. Revercomb,

F.A.C.P., Charleston. Participants and their titles were as follows: Willard Pushkin, M.D. (Assoc.), Charleston, "Geriatrics—Some Considerations"; Charles H. Hiles, M.D., F.A.C.P., Wheeling, "Multiple Myeloma"; Thomas M. Durant, M.D., F.A.C.P., Philadelphia, "The Treatment of Resistant Cases of Congestive Heart Failure"; Howard A. Rusk, M.D., F.A.C.P., New York City, "The Internist in Rehabilitation." A social hour and banquet were held in the evening at the Greenbrier Hotel with Dr. D. A. MacGregor, F.A.C.P., Wheeling, acting as toastmaster. Greetings were extended by Mr. Edward R. Loveland, Philadelphia, Executive Secretary of the College and Dr. Edward L. Bortz, F.A.C.P., Philadelphia, a Regent of the College, gave an address on "Explorations in Medical Education."

The North Dakota Regional Meeting was held at Fargo, Sept. 12, 1953, under the Governorship of Dr. Robert B. Radl. Dr. Howard P. Lewis, Regent, Portland, Ore., was the official guest.

Coming Meetings

ARKANSAS-OKLAHOMA—Tulsa, Sept. 19; A. A. Blair, F.A.C.P., (Ark.) and Wann Langston, F.A.C.P., (Okla.), Governors; Edward L. Bortz, F.A.C.P., Regent, Philadelphia, Official Guest.

OHIO—Dayton, Oct. 9; Charles A. Doan, F.A.C.P., Governor; A. B. Brower, F.A.C.P., General Chairman; LeRoy H. Sloan, F.A.C.P., President, Chicago, Official Guest.

WESTERN NEW YORK—Syracuse, Oct. 9; E. C. Reifenstein, F.A.C.P., Governor; Edward L. Bortz, F.A.C.P., Regent, Philadelphia, Official Guest.

WESTERN PENNSYLVANIA—Pittsburgh, Oct. 9; C. H. Marcy, F.A.C.P., Governor; Walter L. Palmer, F.A.C.P., Regent, Chicago, Official Guest.

KENTUCKY—Louisville, Oct. 10; J. Murray Kinsman, F.A.C.P., Governor; T. Grier Miller, F.A.C.P., Regent, Philadelphia, and Mr. H. Kurtz Canby, Executive Assistant, Philadelphia, Official Guests.

MONTANA-WYOMING—Missoula, Oct. 9–10; Harold W. Gregg, F.A.C.P., Governor; C. C. Sturgis, F.A.C.P., President-Elect, Official Guest.

SOUTHEASTERN (Ala., Fla., Ga., S. C., Cuba)—Sea Island, Ga., Oct. 16–17; Carter Smith, F.A.C.P., Governor for Georgia and General Chairman; W. C. Blake, F.A.C.P., Governor for Florida; E. Dice Lineberry, F.A.C.P., Governor for Alabama; Robert Wilson, F.A.C.P., Governor for South Carolina; J. J. Centurion, F.A.C.P., Governor for Cuba; *LeRoy H. Sloan, F.A.C.P., President, Chicago, Edward R. Loveland, Executive Secretary, Philadelphia, Official Guests.

ARIZONA—Tucson, Oct. 28; Leslie R. Kober, F.A.C.P., Governor; *Philip S. Hench, F.A.C.P., Regent, Rochester, Official Guest.

NEW JERSEY—Trenton, Nov. 4; Edward C. Klein, Jr., F.A.C.P., Governor; Lemuel C. McGee, F.A.C.P., Governor for Delaware and Marshall, Wilmington, Official Guest.

PUERTO RICO—San Juan, Nov. 19, 20, 21; R. Rodriguez-Molina, F.A.C.P., Governor; C. C. Sturgis, F.A.C.P., President-Elect, Mr. Edward R. Loveland, Executive Secretary, Philadelphia, Miss Pearl M. Ott, Executive Assistant, Philadelphia, Official Guests.

MIDWEST (Ill., Ind., Iowa, Minn., Wis.)—Milwaukee, Nov. 21; Karver L. Puestow, F.A.C.P., Governor for Wisconsin; Howard Wakefield, F.A.C.P., Governor for Northern Illinois; C. H. Drenckhahn, F.A.C.P., Governor for Southern Illinois; W. N. Fowler, F.A.C.P., Governor for Iowa; Wesley W. Spink, F.A.C.P., Governor for Minnesota; Francis D. Murphy, F.A.C.P., General Chairman, Milwaukee; LeRoy H. Sloan, F.A.C.P., President, Chicago, and Walter L. Palmer, F.A.C.P., Regent, Chicago, Official Guests.

* Tentative.

NORTH CAROLINA—Chapel Hill, Dec. 3; Elbert L. Persons, F.A.C.P., Governor; Wallace M. Yater, F.A.C.P., Regent, Washington, and Edward R. Loveland, Executive Secretary, Philadelphia, Official Guests.

MICHIGAN—Ann Arbor, Dec. 5; H. Marvin Pollard, F.A.C.P., Governor; LeRoy H. Sloan, F.A.C.P., President, Chicago, and C. C. Sturgis, F.A.C.P., Regent, Ann Arbor, Official Guests.

A.C.P. Postgraduate Courses

In the advertising section of this issue appears the full schedule of courses offered by the American College of Physicians during the autumn and early winter (1953–1954). A detailed Bulletin of these courses may be obtained on request to the Executive Secretary, 4200 Pine St., Philadelphia 4, Pa.

To give wider publicity to one of the new courses somewhat removed from the larger centers of physician population, full details of Course No. 5 are herewith published. Registration forms must be obtained from the Executive Secretary (address above).

COURSE No. 5—PRESENT DAY THERAPY AND ITS PHYSIOLOGICAL BASIS

(November 9–13, 1953)

Department of Medicine
University of Utah College of Medicine
Salt Lake City, Utah

Directors

M. M. Wintrobe, M.D., F.A.C.P.
L. S. Goodman, M.D.

(Minimal Registration, 35;
Maximal Registration, 80)

Fees: A.C.P. Members, $30.00
Non-members, $60.00

Officers of Instruction

Guest Faculty

J. Burns Amberson, M.D., F.A.C.P., Professor of Medicine, Columbia University College of Physicians and Surgeons; Visiting Physician in Charge, Chest Service, Bellevue Hospital, New York, N. Y.

Harry Eagle, M.D., Chief, Experimental Therapeutics, National Microbiological Institute, National Institutes of Health, Bethesda, Md.

Alfred Gilman, M.D., Professor of Pharmacology, Columbia University College of Physicians and Surgeons, New York, N. Y.

University of Utah Faculty

W. R. Christensen, M.D., Professor of Radiology.
H. W. Davenport, M.D., Professor of Physiology.
L. S. Goodman, M.D., Professor of Pharmacology.
M. M. Wintrobe, M.D., F.A.C.P., Professor of Medicine.
G. E. Cartwright, M.D., Associate Professor of Medicine.

H. H. HECHT, M.D., Associate Professor of Medicine.
B. V. JAGER, M.D., Associate Professor of Medicine.
HAROLD BROWN, M.D., Assistant Professor of Medicine.
L. W. JARCHO, M.D., Assistant Professor of Medicine.
JOHN H. MCCLEMENT, M.D., Assistant Professor of Medicine.
C. M. MCNEIL, M.D., Assistant Clinical Professor of Pathology.
F. H. TYLER, M.D., Assistant Professor of Medicine.
A. B. FRENCH, M.D., Instructor in Medicine.
W. R. GAYLOR, M.D., Resident Assistant in Medicine.

One of the objectives of the Committee on Postgraduate Courses of the American College of Physicians is to provide a wide selection of institutions and directors. Another objective is to provide courses to serve its members adequately from a geographical standpoint. This course was selected not only for the above reasons but because of the outstanding qualifications of the faculty and interest in the fine work being done at the University of Utah College of Medicine. The University of Utah faculty is being supplemented by three nationally recognized authorities, Dr. J. Burns Amberson and Dr. Alfred Gilman of Columbia University, and Dr. Harry Eagle of the National Institutes of Health.

There will be daily, except Wednesday, roundtable luncheons from 12 Noon to 1:30 P.M. with Drs. Amberson, Eagle, Gilman, Cartwright, Goodman, Hecht, Jager, Wintrobe and other Officers of Instruction, for informal discussions.

Hotel Accommodations: Hotel Utah, Salt Lake City 10, Utah; Miss Beverly Lippert, Reservation Manager. When writing for reservations identify yourself with the American College of Physicians and this particular course.

TENTATIVE OUTLINE OF COURSE

Monday, November 9

A.M. Session

9:00	Introduction.
9:10– 9:50	Hemolytic Anemias. Dr. Cartwright and Staff.
9:55–10:15	Thrombocytopenic Purpura. Dr. Cartwright and Staff.
10:20–10:50	Physiologic Basis for Splenectomy. Dr. Wintrobe.
10:50–11:30	Roundtable on Splenic Disorders. Drs. Wintrobe, Cartwright and Staff.
12:00– 1:30	Roundtable Luncheon.

P.M. Session

2:00– 3:00	Chemotherapy of Leukemia and Allied Disorders. Dr. Wintrobe.
3:10– 4:30	Roundtable on Hematology. Drs. Wintrobe, Christensen, Cartwright, McNeil and Staff.

Evening

8:00	Tyndale Lecture. Aspects of Chemotherapy of Tuberculosis. Dr. J. Burns Amberson.

Tuesday, November 10

A.M. Session

9:00– 9:50 Pathogenic Mechanisms in Bronchogenic Carcinoma.
Dr. Amberson.

10:00–10:30 Discussion.

10:30–11:10 Disturbances in Alveolar-Capillary Gas Exchange.
Dr. McClement.

11:15–11:30 Discussion.

12:00– 1:30 Roundtable Luncheon.

P.M. Session

Symposium on Pulmonary Emphysema and Its Complications

2:00– 2:20 Diagnosis and Treatment of Pulmonary Emphysema.
Dr. McClement.

2:20– 2:40 Cor Pulmonale.
Dr. Gaylor.

2:40– 3:00 Secondary Polycythemia.
Dr. Hecht.

3:00– 4:30 Roundtable.
Drs. Amberson, Hecht, McClement and Staff.

Evening Social.

Wednesday, November 11

A.M. Session

9:00–10:30 Staff Rounds.

11:00–11:50 Problems of Unresolved Pneumonia.
Dr. Amberson.

11:50–12:30 Discussion.

P.M. Session

Tour of the Laboratories, University, and City.

Evening

8:00 Studies in Mode of Action of Antibiotics.
Dr. Eagle.

Thursday, November 12

A.M. Session

9:00 9:50 Practical Aspects of Antibiotic Therapy.
Dr. Eagle.

10:00–10:50 Synergism and Antagonism of Antibiotics.
Dr. Eagle.

11:00–11:30 Discussion.

12:00– 1:30 Roundtable Luncheon.

P.M. Session

2:00– 2:55 Symposium on Disseminated Lupus Erythematosus
Drs. Jager, Cartwright and Staff.
Detection—L. E. Cells.
Clinical Manifestations.
Hematologic Manifestations.

Symposium on the Therapeutic Uses of ACTH and Cortisone

3:00 Physiologic Basis.
Dr. Tyler.

3:30– 4:30 Roundtable on Therapeutic Indications.
Drs. Gilman, Goodman, Wintrobe, Cartwright, Tyler, French and Staff.

Evening

8:00 The Acidification of the Urine.
Dr. Gilman.

Friday, November 13

A.M. Session

9:00– 9:50 Hypokaliemic Alkalosis.
Dr. Gilman.

10:00–11:30 Roundtable on Diuretics.
Drs. Goodman, Gilman, Davenport, Hecht and Brown.

12:00– 1:30 Roundtable Luncheon.

P.M. Session

2:00– 4:30 Recent Advances in Drug Therapy.
Drs. Goodman, Gilman and Jarcho.

Oral Examinations, American Board of Pediatrics

Oral examinations by the American Board of Pediatrics (Dr. John McK. Mitchell, Executive Secretary, 6 Cushman Rd., Rosemont, Pa.) are scheduled as follows:

Miami, Fla.—October 9, 10 and 11, 1953
Indianapolis, Ind.—December 4, 5 and 6, 1953

The National Gastro-enterological Association will hold its Eighteenth Annual Convention and Scientific Sessions at the Biltmore Hotel, Los Angeles, Calif., on Oct. 12–14, 1953. Following the Convention, Oct. 15–17, the Association's Fifth Annual Course in Postgraduate Gastro-enterology will be given at the Biltmore Hotel and at the College of Medical Evangelists in Los Angeles, the course being under the direction of Drs. Owen H. Wangensteen, of Minneapolis, Minn., and I. Snapper, of Chicago, Ill.

Graduate Fortnight, New York Academy of Medicine

The 26th Annual Graduate Fortnight of the New York Academy of Medicine will be held at its headquarters, 2 East 103rd St., New York City, Oct. 19–30, 1953, the program being devoted to "Disorders of the Blood and the Blood-Forming Organs." The program consists of six morning panels held at the Academy, twenty hospital clinics at local hospitals and at the Academy, ten evening sessions at the Academy and a scientific exhibit at the Academy.

Fellows of the New York Academy of Medicine are admitted free. A registration card will be sent to non-members upon receipt of check, payable to the New York Academy of Medicine for $10.00 for the entire program, or $5.00 for the second

week. Medical officers of the Armed Services, in uniform, will be admitted without charge.

Among the scheduled evening speakers are included the following Fellows of the College: Drs. William B. Castle, Maxwell M. Wintrobe, R. Janet Watson, Eugene L. Lozner, Charles A. Doan, Louis R. Wasserman, William Dameshek, and Leon O. Jacobson. These and many other members of the College appear on the program of panels and hospital clinics.

Annual Meeting, American Academy of Pediatrics

The American Academy of Pediatrics will hold its 22nd Annual Meeting at Miami, Fla., Oct. 4–9, 1953. Among the speakers appear Dr. Walter O. Klingman, F.A.C.P., Charlottesville, Va.; Dr. Edward P. Cawley (Associate), Charlottesville, Va.; Dr. David H. Clement, F.A.C.P., New Haven, Conn.

Annual Meeting, American Psychosomatic Society

The American Psychosomatic Society will hold its 11th Annual Meeting at the Jung Hotel, New Orleans, March 27–28, 1954. The Program Committee would like to receive titles and abstracts of papers for consideration for the program by December 1, 1953. The Committee is particularly interested in investigations in the theory and practice of psychosomatic medicine as applied to adults and children in all the medical specialties, and in contributions in psychophysiology and ecology. Abstracts should be submitted in quadruplicate to the Chairman of the Program Committee, Dr. George L. Engel, 551 Madison Ave., New York 22, N. Y.

Proctologic Research Fellowship

The International Academy of Proctology has announced the establishment and award of a one-year Proctologic Research Fellowship in the amount of $1,200.00. The Research Fellowship grant has been awarded to the Jersey City Medical Center, N. J., to be administered under the direction of the Surgical Director. Another similar grant will be announced at the next annual meeting of the Academy.

Dr. Alexander B. Gutman, F.A.C.P., and others, with the assistance of the staff at Mount Sinai Hospital, will conduct a one-week postgraduate course in "Present-Day Methods in Medical Practice," Oct. 12–17, 1953, at Mount Sinai Hospital. The course is given in affiliation with Columbia University. The matriculation fee will be $75.00. Details and application forms may be obtained from the Registrar for Medical Instruction, Mount Sinai Hospital, New York 29, N. Y.

Endocrine Society Announces Postgraduate Assembly in Endocrinology and Metabolism

The Endocrine Society and the University of Minnesota announce a Postgraduate Assembly in Endocrinology and Metabolism for Physicians, the Sixth Annual Assembly sponsored by the Endocrine Society, which will be presented on the University of Minnesota campus from September 28 to October 3, 1953. Lectures will

be held in the Museum of Natural History Auditorium, while the facilities of the immediately adjacent Center for Continuation Study will be available for demonstrations and for the accommodation of registrants for the course.

Faculty for the Assembly includes outstanding authorities in the field of endocrinology from various parts of the country as well as members of the faculty of the University of Minnesota Medical School and the Mayo Foundation. The program will be presented under the direction of Dr. Edward C. Reifenstein, Jr., F.A.C.P., Oklahoma City, General Chairman for The Endocrine Society, and Dr. Cecil J. Watson, F.A.C.P., Professor and Head of the Department of Medicine of the University of Minnesota Medical School.

International Symposium on Cardiovascular Regulations

An International Symposium on Cardiovascular Regulations, sponsored by the University of Vermont College of Medicine and the New Hampshire and Vermont Heart Associations, is being held at Burlington, Vt., Sept. 8–12, 1953. Dr. Wilhelm Raab, F.A.C.P., University of Vermont College of Medicine, Burlington, Vt., has charge of program arrangements. Speakers appear from Egypt, Argentina, Chile, England, Sweden, Germany and the United States. The Symposium lasts from September 8–10 and two Cardiac Seminars are given from Sept. 10 to 12. Guest speakers on the Cardiac Seminars include Drs. C. E. Kossmann, F.A.C.P., New York University; Harold B. Levine, F.A.C.P., Harvard Medical School; Dr. Wilhelm Raab, F.A.C.P., University of Vermont, and Dr. Irvine H. Page, F.A.C.P., Cleveland Clinic Foundation.

Research Applications Accepted by American Heart Association

Applications are now being accepted for research awards to be made during the coming year under the joint auspices of the American Heart Association and its affiliates throughout the country, according to an announcement by Dr. Irving S. Wright, F.A.C.P., Chairman of the Association's Scientific Council. Applications for research fellowships should be sent to the Association by September 15, 1953, and applications for research grants-in-aid should be filed by December 1, 1953. Information and forms may be obtained through the Medical Director, American Heart Association, 44 E. 23rd St., New York 10, N. Y.

Van Meter Prize Award

The American Goiter Association, through its recording secretary, Dr. John C. McClintock, Albany, N. Y., again announces the Van Meter Prize Award of $300.00 and two honorable mentions for the best essay submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the Association at Boston, Mass., April 29-May 1, 1954, provided essays of sufficient merit are presented in competition. The competing essays may cover either clinical or research investigation; should not exceed 3,000 words in length; must be presented in English, and a typewritten, double spaced copy in duplicate sent to the Corresponding Secretary, 149½ Washington Ave., Albany 10, N. Y., not later than January 15, 1954. A place will be reserved on the program at the annual meeting for the presentation of the prize award essay by the author, if it is possible for him to attend.

The James Picker Foundation for Radiological Research

Since 1947, the James Picker Foundation for Radiological Research has provided funds for advanced research to further and broaden the uses of radiology for the good of mankind. Grants have been made to institutions in various parts of the world and also to individuals. Projects offering promise of improvement in radiological methods of diagnosis or treatment of disease are eligible for assistance from the Foundation.

Applications for grants-in-aid and fellowships should be directed to the James Picker Foundation, Inc., Hanover Bank Trustee, 70 Broadway, New York 4, N. Y., or to the Secretary, Division of Medical Science, National Research Council, 2101 Constitution Ave., N.W., Washington 25, D. C.

The Damon Runyon Memorial Fund for Cancer Research, since its inception in 1946, has made nation-wide grants totalling $6,708,347.00 to 246 fellows and 166 institutions in 46 states and the District of Columbia and in 14 foreign countries. The largest institutional grant for May, 1953, $46,000.00, went to the Memorial Center for Cancer and Allied Diseases, New York City, for two projects under the direction of Dr. Cornelius P. Rhoads, F.A.C.P., namely "Studies on Serum Iodide and Serum Protein in Relation to Thyroid Function and to Treatment with Radioiodine" and "Clinical Studies of Viruses as Antineoplastic Agents."

Grants by National Foundation for Infantile Paralysis

The National Foundation for Infantile Paralysis has announced the approval of research and professional and educational projects totaling $2,283,384.00, which took effect July 1, 1953. The awards go to 21 medical schools, hospitals, research institutions and educational organizations in the United States.

Of the total authorized, $762,380.00 was allocated for research seeking means of preventing the disease and for improved methods of treatment, and $1,521,004.00 for programs in professional education.

This action brings to $50,000,000.00 the amount provided in March of Dimes funds since 1938 for the study of medical care problems, aid to professional education and the support of polio research. Since 1938 the organization has expended an additional $148,000,000.00 in meeting the costs of treatments for those patients who required assistance.

It has made a grant of $120,000.00 to the University of Pennsylvania School of Medicine, where a new rehabilitation center for aid of the physically handicapped will shortly be put into operation. A commission on rehabilitation composed of the department heads in the Medical School and Hospital of the University of Pennsylvania will direct the center, and Dr. George Morris Piersol, M.A.C.P., will be Chairman. The Coördinator of Rehabilitation will be Dr. William Dunbar (Associate), Associate in Medicine, Public Health and Preventive Medicine at the University.

Grants for Research on Vitamins and Nutrition

The National Vitamin Foundation has announced fourteen new grants to twelve universities and two hospitals for research on vitamins and nutrition, amounting to $69,710.00, bringing the total appropriation by the Foundation since its incorporation in 1946, to $704,890.50. The Foundation also has appropriated more than $135,000.00 in additional funds for education and public health purposes. Its headquarters is at 150 Broadway, New York 38, N. Y.

Second Annual Tuberculosis Symposium, Saranac Lake

The Second Annual Tuberculosis Symposium for General Practitioners was held at Saranac Lake July 13–17, and was attended by forty family doctors from the United States and Canada. This annual refresher course is approved by the American Academy of General Practitioners for twenty-six hours of formal credit and is sponsored by the Saranac Lake Medical Society and the Adirondack Counties Chapter of the New York State Academy of General Practice.

The faculty is composed of physicians and scientists from Saranac Lake and the surrounding sanatoria and rehabilitation clinics, including the following Fellows of the American College of Physicians: Dr. Frederick Beck, Director of Ray Brook State Tuberculosis Hospital; Dr. Daniel M. Brumfiel, Saranac Lake; Dr. Joseph Gordon, Ray Brook; Dr. John N. Hayes, Medical Director of Sanatorium Gabriels; Dr. Roger S. Mitchell, Associate Medical Director of Trudeau Sanatorium; Dr. James Monroe, Ray Brook; Dr. Edward N. Packard, Saranac Lake; and Dr. Arthur J. Vorwald, Head of the Trudeau Foundation and Saranac Laboratory.

The following faculty members are Associates of the College: Dr. Gordon M. Meade, Medical Director of Trudeau Sanatorium; Dr. E. Osborne Coates, Jr., Assistant Medical Director of Trudeau Sanatorium; and Dr. Giles F. Filley, Associate Physiologist of the Trudeau Foundation.

American Heart Association Marks Anniversary

The American Heart Association has marked its fifth anniversary as a voluntary health agency by awarding, jointly with its affiliates, an additional $473,930.00 for 89 research grants-in-aid in the field of heart and blood vessel diseases, according to a recent announcement by Dr. Robert L. King, F.A.C.P., President of the Association. These latest awards increase to a grand total of almost six and one half million dollars, the sum spent for research studies by the American Heart Association and its affiliated state and local societies over the five-year period.

Incorporated in 1924 as a scientific body with a professional membership, the American Heart Association became a voluntary health agency in 1948, admitting laymen to its governing bodies and initiating an annual fund-raising campaign to finance research, professional and public education programs, and community service activities.

The following members of the American College of Physicians will address the Tennessee Valley Medical Assembly at Chattanooga, Tenn., Sept. 28–29: Dr. Paul D. White, F.A.C.P., Boston, "Hypertensive Heart Disease a Generation Ago and Now" and "Notes on Coronary Heart Diseases"; Dr. John R. Youmans, F.A.C.P., Nashville, Tenn., "Anemia and Nutrition"; Dr. V. P. Sydenstricker, F.A.C.P., Augusta, Ga.; Dr. Paul Holbrook, F.A.C.P., Tucson, Ariz., "Treatment of Rheumatoid Arthritis."

Dr. Henry D. Diamond, (Associate), New York City, presented a paper entitled "Treatment of Special Complications of Lymphomas and Leukemias" and participated in a symposium on hematuria on the program of the Rocky Mountain Cancer Conference at Denver, July 8–9, 1953, the conference being sponsored by the Colorado State Medical Society. Dr. Lumir R. Safarik, F.A.C.P., President of the Denver Medical Society, presided over one of the sessions.

The scientific sessions of the annual meeting of the West Virginia State Medical Association, held July 23–25 at White Sulphur Springs, was opened with a symposium on pain. Dr. Oscar B. Biern, F.A.C.P., Huntington, W. Va., was moderator of the symposium, and Dr. Bayard T. Horton, F.A.C.P., Rochester, Minn., a participant, presented "Headache: General Consideration." Dr. Pat A. Tuckwiller, F.A.C.P., Charleston, W. Va., presided at the clinical pathological conference. Participating in the symposium on emergencies in general practice were Dr. Thomas M. Durant, F.A.C.P., Philadelphia, "Cardiovascular Emergencies in General Practice," and Dr. Edward L. Bortz, F.A.C.P., Philadelphia, "Medical Emergencies in Senior Citizens." At the final session, Dr. Howard A. Rusk, F.A.C.P., New York City, presented "A Doctor's Responsibility in the Changing Order."

Army Civilian Medical Consultants

Maj. Gen. George E. Armstrong, F.A.C.P., Army Surgeon General, recently announced the names of seventeen civilian physicians who have been selected as senior civilian consultants to the Surgeon General, beginning July 1, 1953. The consultants are chosen with the assistance of the Society of U. S. Medical Consultants, subject to the approval of Gen. Armstrong. Each consultant must have outstanding abilities as a teacher, must be certified by the specialty board in his field, and, preferably, should have had some military service as a medical officer. Among the medical consultants selected are the following Fellows of the College: Dr. Worth B. Daniels, F.A.C.P., (Internal Medicine), Clinical Professor of Medicine, Georgetown University School of Medicine, Washington, D. C.; Dr. George P. Robb, F.A.C.P., (Cardiology), Assistant Medical Director, Metropolitan Life Insurance Company, New York, N. Y.; Dr. John W. Trenis, F.A.C.P., (Tuberculosis), Associate in Medicine, George Washington University School of Medicine, Washington, D. C.; Dr. Frank H. Krusen, F.A.C.P., (Physical Medicine), Head, Section on Physical Medicine, Mayo Clinic, Rochester, Minn.; Dr. W. C. Menninger, F.A.C.P., (Psychiatry and Neurology), Director, Menninger Foundation, Topeka, Kans.; Dr. Byrl R. Kirklin, F.A.C.P., (Radiology), Chief Radiologist, Department of Radiology, Mayo Clinic, Rochester, Minn.

New Dean at Johns Hopkins University School of Medicine

Philip Bard, Ph.D., Professor of Physiology at the Johns Hopkins University School of Medicine, Baltimore, has been appointed Dean of the Medical Faculty, succeeding Dr. Alan N. Chesney, who served nearly 25 years as Dean. Dr. Chesney will continue his association with Johns Hopkins institutions in an emeritus capacity.

Dr. Robert Wilson, F.A.C.P., Charleston, S. C., is Secretary of the South Carolina Medical Association. He is the Governor of the American College of Physicians for South Carolina and a member of the A.C.P. Committee on Credentials.

Colonel Leedham Receives Legion of Merit

Col. Charles L. Leedham (MC), F.A.C.P., was awarded the Legion of Merit by Maj. Gen. George E. Armstrong, F.A.C.P., Army Surgeon General, at ceremonies on Friday, June 26. Col. Leedham, presently assigned as Chief of the Education and Training Division, Office of the Surgeon General, received the decoration for "ex-

ceptionally meritorious conduct in the performance of outstanding service as Consultant to the Chief Surgeon" in the Far East from Nov. 1, 1951 to April 30, 1953. The citation also states that Col. Leedham "contributed materially to the research into hemorrhagic fever by expediting critical supplies, making available highly specialized personnel, and offering constant guidance and encouragement to the research team of medical scientists investigating the disease."

During Col. Leedham's 24-year Army career, dating back to 1929, he has held many positions of responsibility, both in the Continental United States and in overseas commands. Besides the Legion of Merit, he also holds the Bronze Star Medal and the Commendation Ribbon with Medal Pendant.

Rear Adm. Bartholomew W. Hogan, (MC), USN, F.A.C.P., has been recently detached as Commanding Officer of the U. S. Naval Hospital, Naval Medical Center, Bethesda, Md., and transferred to the Staff, Headquarters, Commander in Chief, Pacific Fleet, Honolulu, T. H.

Adm. Hogan has been relieved as Commanding Officer of the U. S. Naval Hospital at Bethesda by Capt. Gordon B. Tayloe, (MC), USN, F.A.C.P., who was previously on duty as Commanding Officer of the U. S. Naval Hospital, Portsmouth, Va.

Capt. Dunne W. Kirby, (MC), USN, F.A.C.P., heretofore Senior Assistant Medical Officer at the Great Lakes Naval Training Center, reported for duty August 9, 1953, at the U. S. Naval Hospital, Bainbridge, Md., as Chief of Medicine.

Dr. Clifton K. Himmelsbach, F.A.C.P., has been appointed Assistant Chief, Division of Hospitals, Public Health Service, Department of Health, Education, and Welfare, Washington, D. C. He succeeds Dr. Myron D. Miller, F.A.C.P., who has recently been assigned as Medical Officer in Charge of the U. S. Public Health Service Hospital, Seattle, Wash. Dr. Himmelsbach's new responsibilities involve the administration of 16 hospitals and 125 outpatient facilities that comprise the medical care program for legal beneficiaries of the Public Health Service.

For her work for women physicians, Dr. Elizabeth Bass, F.A.C.P., Lumberton, Miss., received the Elizabeth Blackwell Memorial Award, a gold medal, of the American Medical Women's Association at a dinner at the Barbizon-Plaza Hotel in New York, May 31. Prior to her retirement, Dr. Bass was Associate Professor of Clinical Medicine at Tulane University School of Medicine and had previously served as Professor of Clinical Laboratory Diagnosis at Tulane University Graduate School of Medicine.

Dr. Thomas S. Lee, F.A.C.P., Washington, D. C., founder and permanent Honorary President of the Washington Heart Association, recently received a medal and High Citation Certificate from the American Legion for his work with the Washington Heart Association.

At the annual meeting of the National Association of Methodist Hospitals and Homes, Dr. Malcolm Thomas MacEachern, F.A.C.P., Chicago, received the honor of being named to the Methodist Hall of Fame in Philanthropy.

Medical Society of New Jersey Issues Plaques to Members

The Medical Society of New Jersey is the oldest medical society in the Western Hemisphere. Its President is Dr. Harrold A. Murray, F.A.C.P., Newark. To each of its almost 6,000 members the Society has issued a plaque testifying to his membership in the Society, but acting as a reminder both to the member and to his patient that the physician has a solemn duty to his patient and to his community. The plaque is part of the Society's continuing effort to maintain and improve medical public relations. Designed for prominent display in the doctor's office, the plaque constitutes a public pledge which reads: "Be it known to all! Dr. John Doe is a member of The Medical Society of New Jersey and is therefore pledged to uphold the highest standard of practice in the tradition of his chosen profession. Hence, fees within the patient's ability to pay; dependability to render needed services; participation in community activities together with his fellow citizens are constantly his special concern. His earnest desire is to improve patient-doctor relationship at every turn."

Dr. Lee E. Sutton, Jr., F.A.C.P., in tribute to his twenty-five years' service with the Medical College of Virginia, was honored during the past spring at a banquet at the Commonwealth Club of Richmond. Dr. Sutton was presented a silver punch bowl with appropriate engraving.

Drs. Josephine B. Neal, F.A.C.P., New York City, and Ellen C. Potter, F.A.C.P., Trenton, N. J., recently were presented with the Elizabeth Blackwell Citations of the New York Infirmary. Dr. Neal was for many years in charge of the Division of Acute Infections of the Central Nervous System of the Department of Health of New York City and also served as Associate Director of the Laboratories of the Health Department. Dr. Potter was formerly Secretary of Welfare of the State of Pennsylvania, the first woman cabinet officer in any state. Later she became Director of Medicine, Department of Institutions and Agencies, of New Jersey, served as President of the American Medical Women's Association, President of the National Conference of Social Work and Acting President of the Woman's Medical College of Pennsylvania.

Dr. James J. Waring, M.A.C.P., Emeritus Professor of Medicine, University of Colorado School of Medicine, was the recipient of the Trudeau Medal for medical achievement in tuberculosis, and Dr. James R. Rueling, F.A.C.P., Bayside, N. Y., Speaker of the A.M.A. House of Delegates, was the recipient of the Will Ross Medal for distinguished service in the tuberculosis movement in a field other than the medical sciences, at the recent annual meeting of the National Tuberculosis Association.

Dr. R. Hugh Wood, F.A.C.P., Dean of Emory University School of Medicine, received an honorary degree at the last commencement exercises of the Medical College of Virginia.

Dr. James J. Waring, M.A.C.P., Denver, President of the Board of Trustees of the Gerald Webb Memorial Laboratory, recently announced that private contributions have set up an endowment of $200,000.00. Cornerstone laying ceremonies for the Laboratory were recently held at the University of Colorado Medical Center. The $150,000 structure is being built by the Colorado Foundation for Research in Tuberculosis, established twenty-nine years ago in Colorado Springs by the late Dr.

Webb and supported by private contributions from his friends and former patients. Research under way is concerned with evaluating present antibiotics for tuberculosis, developing a faster method for culturing the tubercle bacillus, and studying new antibiotics. Dr. Webb was a Fellow and former Regent of the American College of Physicians.

Dr. Paul F. Dickens, F.A.C.P., has become Professor Emeritus (Medicine) at George Washington University School of Medicine, Washington, D. C. Dr. Dickens, who had served as Clinical Professor of Medicine since 1929, was also Professor of Medicine at the U. S. Naval Medical School from 1925 to 1938.

Dr. Robert Hanna Felix, F.A.C.P., Director of the National Institute of Mental Health, Bethesda, was awarded the honorary degree of Doctor of Science in June by Boston University School of Medicine.

The University of Louisville School of Medicine has established a new chair in the Department of Internal Medicine to be known as the John Walker Moore Professorship of Medicine. Dr. Moore, now deceased, was the former Dean and was a Fellow of the American College of Physicians.

Dr. Chester N. Frazier, F.A.C.P., Boston, Mass., and Dr. Hyman I. Goldstein (Associate), Camden, N. J., appeared on the program of the International Congress for the History of Science, held in Jerusalem during the first week of August. Dr. Frazier's title was "Medicine in the New Harmony of Robert Owen—1825–1827;" Dr. Goldstein's title was "Errors of Priority Credit in Medicine."

Dr. Walter C. Alvarez, F.A.C.P., Professorial Lecturer in Medicine, University of Illinois College of Medicine, recently delivered the Frederick Robert Zeit Memorial Lecture, sponsored by Alpha Kappa Kappa Fraternity, in Thorne Hall of Northwestern University, Chicago. His subject was "Some Problems in Modern Diagnosis."

Dr. Leon Unger, F.A.C.P., Chicago, recently returned from a lecture tour of Hawaii, Japan, Hong Kong, Siam, Pakistan, India, Israel and Greece. His lectures dealt with bronchial asthma and migraine and were delivered before medical societies in various cities of the countries named.

Dr. Russell Wilder, F.A.C.P., Director of the National Institute of Arthritis and Metabolic Diseases at Bethesda, Md., retired on July 1 for reasons of health. Dr. Wilder became the first Director of the National Institute of Arthritis and Metabolic Diseases shortly after its creation in 1950. Before serving with the Arthritis Institute, Dr. Wilder was with the Mayo Foundation and Clinic at Rochester, Minn., 1919–50. He has now returned to his home in Rochester.

Dr. Maurice Sokolow, F.A.C.P., Associate Professor of Medicine, University of California School of Medicine, San Francisco, is currently on sabbatical leave, working in London, England, with Professor George Pickering at St. Mary's Hospital and with Dr. Paul Wood, Director of the Institute of Cardiology.

Dr. Anton S. Yuskis (Associate), San Diego, Calif., has been made the first honorary President of the San Diego County Heart Association.

Dr. Benjamin Jeffries, F.A.C.P., Detroit, was recently elected Secretary of the Michigan Society of Neurology and Psychiatry.

Dr. Philip H. Jones, F.A.C.P., New Orleans, is President of the Louisiana State Medical Society.

Dr. Nils P. Larsen, F.A.C.P., has been elected President-Elect of the Hawaii Territorial Medical Association. Dr. Larsen is the College Governor for Hawaii and resides in Honolulu.

Dr. Arthur C. Curtis, F.A.C.P., Ann Arbor, Mich., has been elected President of the Society for Investigative Dermatology.

Dr. Carl H. Gellenthien, F.A.C.P., Valmora, N. M., has been elected a Vice President of the American Academy of Tuberculosis Physicians.

Dr. Earl C. Elkins, F.A.C.P., Rochester, Minn., has been elected Secretary-Treasurer of the American Board of Physical Medicine and Rehabilitation.

Dr. Henry H. Turner, F.A.C.P., Oklahoma City, is a member of the Council of the Southern Medical Association from Oklahoma, to serve a regular term of five years.

Dr. Oscar B. Biern, F.A.C.P., Huntington, W. Va., has been appointed by Gov. William C. Marland as a member of the Medical Licensing Board of that state for a five-year term to succeed Dr. Walter E. Vest, F.A.C.P., also of Huntington.

Dr. George C. Andrews, F.A.C.P., New York City, was elected Vice President and Dr. J. Lamar Callaway, F.A.C.P., Durham, N. C., was elected Secretary of the American Dermatological Association at the annual scientific session held in Lake Placid, N. Y.

At the annual convention of the American College of Cardiology, Dr. Philip Reichert, F.A.C.P., New York City, was elected Secretary, and Dr. Seymour Fiske, F.A.C.P., New York City, was elected Treasurer.

The American College of Chest Physicians, at its annual meeting held in New York, elected Dr. Alvis E. Greer, F.A.C.P., Houston, Tex., President. Dr. James H. Stygall, F.A.C.P., Indianapolis, Ind., and Dr. Herman J. Moersch, F.A.C.P., Rochester, Minn., were elected Vice Presidents.

Florida Clinical Diabetes Association

At the First Annual Meeting of the Florida Clinical Diabetes Association, May 14–15, 1953, St. Petersburg, Fla., Dr. Fred Mathers, F.A.C.P., Orlando, was elected

President, Dr. Sidney Davidson, F.A.C.P., Lake Worth, Vice President, and to the Board of Directors Dr. T. Z. Cason, F.A.C.P., Jacksonville, Dr. Richard H. Sinden (Associate), St. Petersburg, were selected.

Dr. Carl Nadler, Jr., (Associate), has been advanced to Assistant Professor of Clinical Medicine at Tulane University School of Medicine recently.

Dr. William R. Jordan, F.A.C.P., Richmond, Va., Dr. William M. Nicholson, F.A.C.P., Durham, N. C., and Dr. Robert Wilson, F.A.C.P., Charleston, S. C., appear on the Editorial Board of the newly founded *Tri-State Journal*, official publication of the Tri-State Medical Association of the Carolinas and Virginia.

Col. Francis W. Pruitt, F.A.C.P., has arrived at Walter Reed Army Medical Center, Washington, D. C., for assignment as Medical Service Chief of its Walter Reed Army Hospital component. He succeeds Col. Paul S. Fancher, F.A.C.P., who has been transferred to the Far East Command. Col. Pruitt's previous station for the past eighteen months was the Letterman Army Hospital, San Francisco, Calif.

At the annual meeting of the Chicago Society of Internal Medicine, May 25, 1953, Dr. Richard B. Capps, F.A.C.P., was elected President; Dr. Arthur R. Colwell, F.A.C.P., Vice President; Dr. Edwin N. Irons, F.A.C.P., Secretary-Treasurer; and Drs. Howard L. Alt, F.A.C.P., Frank B. Kelly, F.A.C.P., and Lowell R. Coggeshall, F.A.C.P., were elected to the Executive Committee.

Dr. Hirsch L. Gordon, (Associate), New York, N. Y., has been appointed Associate in Psychiatry, New York Medical College, Flower and Fifth Avenue Hospitals, and has been elected a Fellow of the American Psychiatric Association.

Dr. Harold D. Levine, F.A.C.P., was recently elected President of the newly formed Greater Boston Chapter of the Massachusetts Heart Association.

Dr. Giles F. Filley (Associate), has been appointed Head of the Physiology Department of the Trudeau Sanatorium and Foundation, Saranac Lake, N. Y., succeeding Dr. George W. Wright, who resigned to join the staff of St. Luke's Hospital, Cleveland, Ohio. Dr. Filley is a graduate of Williams College and of Johns Hopkins University School of Medicine, and is a diplomate of the American Board of Internal Medicine.

Dr. Robert Collier Page, F.A.C.P., General Medical Director of the Standard Oil Company, New York City, recently became President-Elect of the Industrial Medical Association. Dr. Page recently addressed the Economic Club of Detroit on the subject "Where Do We Stand Now in Regard to Socialized Medicine and Private Enterprise in Providing Adequate Health for All Our People throughout the United States?"

OBITUARIES

DR. JOHN DELBERT ADCOCK

Dr. John Delbert Adcock, F.A.C.P., Assistant Professor of Internal Medicine, University of Michigan Medical School, died on May 10, 1953.

Dr. Adcock was born on Jan. 11, 1909, in Warrensburg, Missouri, and received his A.B. degree at the University of Missouri in 1931. He received his medical degree from the University of Pennsylvania School of Medicine in 1935 and he interned at the University of Pennsylvania Hospital in Philadelphia from 1936 to 1938.

Following this, he became a Resident in the Tuberculosis Unit of the University Hospital, Ann Arbor, Michigan, from 1938 to 1939, and a Resident in Internal Medicine in the same institution from 1939 to 1940.

He then moved to Philadelphia, where he was Assistant Physician from 1941 to 1942, as well as Assistant Physician on the Tuberculosis Service of the Philadelphia General Hospital. During this time he also served as Assistant Instructor, and subsequently Instructor, of Internal Medicine at the University of Pennsylvania School of Medicine.

He was then invited to return to the University of Michigan Medical School as Assistant Professor of Internal Medicine, in which capacity he had served since 1943.

Dr. Adcock was highly respected as an internist by his colleagues. His primary interest lay in the study of infectious diseases, especially those caused directly or indirectly by the tubercle bacillus. In this field he conducted important research, combining clinical with laboratory work, which resulted in numerous valuable papers published in professional journals. Notable among these was a basic study of streptomycin, which was made possible by his having been designated as one of the physicians to receive a supply of the drug when it first became available in 1945. Between 1946 and 1951 he directed for the United States Public Health Service an investigation of the treatment of tuberculosis with various antimicrobials and, more recently, he had conducted studies of the chemotherapy of a number of diseases of microbic origin.

Dr. Adcock was a member of the American Trudeau Society, the Michigan Trudeau Society and the American Medical Association. He was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1943.

All those who knew Dr. Adcock and who understood the difficulties to which a precarious state of health constantly subjected him will join in admiration for his accomplishments and in sincere sorrow for his loss. He leaves his widow, the former Margaret Cowie, of Ann Arbor, and a son, John, aged seven.

H. M. Pollard, M.D., F.A.C.P.,
Governor for Michigan

DR. CORNELIUS OLIVER BAILEY

Dr. Cornelius Oliver Bailey, F.A.C.P., was born at Quinlan, Tex., Feb. 11, 1887. He attended State Teachers College, Huntsville, Tex., and the University of Texas at Austin. He received his M.D. degree from the University of Texas School of Medicine, 1915, and thereafter pursued graduate work in the U. S. Army Medical School. He also held the degrees of A.B. (1936) and A.M. (1937) from the University of Southern California and had done postgraduate work in the clinics and institutions of Boston, New York and Vienna.

Dr. Bailey interned at the Cleveland City Hospital, 1915–16, and then became a medical officer in the U. S. Army, serving in various Army installations in the United States and also at the U. S. Army Base Hospital in Coblenz, Germany, in 1921. He was discharged from the regular Army in 1922 with the rank of Major.

Thereafter he became Director of the Department of Radiology at St. Paul's Hospital (1925–30) and Consulting Radiologist to the Parkland Hospital, both of Dallas, Tex. He removed to California in 1931 and became, successively, Instructor, Assistant Professor and Professor Emeritus of Roentgenology at the College of Medical Evangelists. He had served as a member of the staff of the Cedars of Lebanon, California Lutheran, White Memorial and Beverly Hospitals and the Methodist Hospital of Southern California.

Dr. Bailey was a Diplomate of the American Board of Radiology, a member of the Radiological Society of North America, the Southern Medical Association, the American Medical Association, and had been a Fellow of the American College of Physicians since 1929.

DR. WALTER BOOTHBY

Dr. Walter Boothby, F.A.C.P., emeritus member of the Mayo Clinic staff and Emeritus Professor of Medicine of the University of Minnesota, died July 3, 1953. Dr. Boothby achieved distinction in the field of aviation, physiology and medicine. The foundations for his later pioneering work on the Mayo staff were laid in Boston. He was born in Boston on July 28, 1880. After completing his undergraduate and graduate work at Harvard, he interned at the Boston City Hospital, and then practiced surgery for seven years. He directed the work of the metabolism laboratory at the Peter Bent Brigham Hospital from 1913 to 1916. He was instructor in anatomy at Harvard from 1910 to 1916, and lecturer in anesthesia from 1914 to 1916. All of this background appeared to fit him for his appointment as head of the Section of Metabolism in the Mayo Clinic, a position which he assumed in November 1916. During World War I he served in France with the A.E.F. for twenty-two months as a Captain and Major in the Medical Corps. Serving for the greater part of his time in the Gas Defense Service, he acted also as a chief of a surgical team in the St. Mihiel and Argonne battles. During World War II, he headed the Section on Aviation Medicine and Research, Mayo Foundation, and in 1948 he became an emeritus member of the staff. Retirement did not mean the end of his interest in aviation medicine. He immediately accepted the appointment as guest Professor at the University of Lund, Sweden, and in 1949 he became Consultant to the Swedish Committee on Naval and Aviation Medicine. In 1950, he became a member of the staff of the Randolph Field School of Aviation Medicine, San Antonio, Texas. He later affiliated with the Lovelace Clinic in Albuquerque, New Mexico.

Dr. Boothby's versatility was reflected in his membership in various scientific organizations. He was certified by the American Board of Internal Medicine. He was not only a Fellow of the American College of Physicians, but of the American College of Surgeons as well. He held memberships in the Aero Medical Association of the United States, the Institute of Aeronautical Sciences, the Massachusetts Medical Society, the American Physiological Society, the American Society of Biological Chemists, the American Society for Clinical Investigation, the Society for Experimental Biology and Medicine, the American Medical Association, the American Institute of Nutrition, American Society for Experimental Pathology, the American Society for Pharmacology and Experimental Therapeutics and the Association of American Physicians.

WESLEY W. SPINK, M.D., F.A.C.P.,
Governor for Minnesota

DR. RALPH P. DANIELLS

Dr. Ralph Peabody Daniells (Associate) of Toledo, Ohio, died April 19, 1953, of acute coronary thrombosis in the Toledo Hospital, where he had been a member of the staff for many years.

Born in 1874, Dr. Daniells had attended the University of Wisconsin, where he was graduated with the degree of Bachelor of Science, and Rush Medical College, Chicago, from which he received his M.D. degree in 1899. Most of his active medical life was spent in Toledo, where he was formerly on the staff of the Mercy Hospital. During World War II, he had served as a Major in the U. S. Public Health Service.

Dr. Daniells was a member of his local and state societies and of the American Medical Association. He became a member of the American Congress on Internal Medicine in 1924 and had been an Associate of the American College of Physicians since 1926, when the Congress and the College merged.

DR. KENNETH F. GLAZE

Kenneth F. Glaze, M.D., F.A.C.P., staff physician at the Hospital of the Veterans Adminstration Center, Temple, Texas, died April 6, 1953.

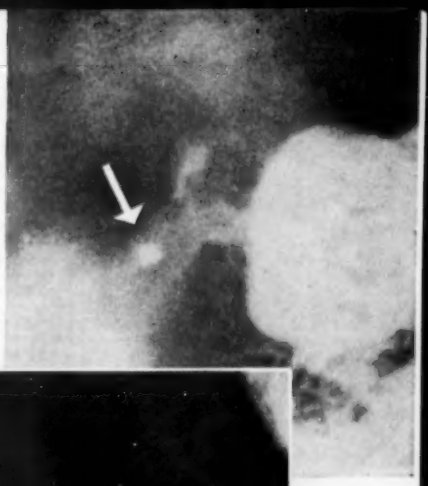
Dr. Glaze was born in Missouri, July 23, 1898. He attended the University of Missouri and later St. Louis University, from which he received his B.S and M.D. degrees (1923). He served his internship at St. Luke's Hospital, St. Louis, followed by a residency of one year at the same hospital.

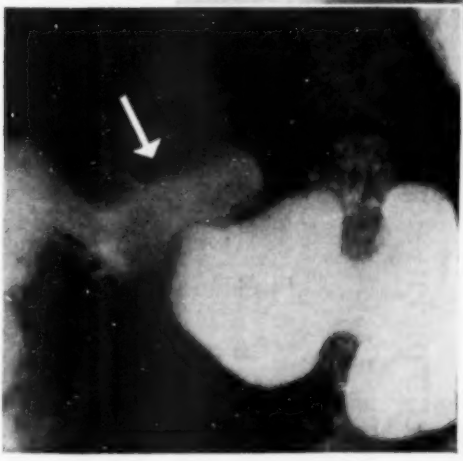
Dr. Glaze then engaged in the private practice of Internal Medicine in St. Louis from 1925 until 1951 when he accepted full-time appointment as a staff physician in the Department of Medicine and Surgery, Veterans Administration. He was assigned to the Veterans Administration Hospital, Temple, Texas, where he served in the capacity of Admitting Physician until the time of his death.

During his years of practice in St. Louis, Dr. Glaze held staff appointments at St. Luke's Hospital and at various times also held appointments at Missouri Baptist Hospital, St. Mary's Hospital and Barnes Hospital, all in St. Louis. He held appointment from 1925 to 1943 as Instructor in Clinical Medicine at Washington University School of Medicine. Dr. Glaze was a member of the St. Louis Medical Society, Missouri State Medical Association, American Medical Association, and the Southern Medical Association. He became a Fellow of the American College of Physicians in 1939.

The death of Dr. Glaze is noted with regret by his many friends and colleagues.

J. T. Boone, Vice Admiral (M.C.) U. S. Navy, Rtd.
Chief Medical Director
Governor for the Veterans Administration





Top left: "X-rays revealed a huge ulcer crater in the duodenal bulb."

Top right: "Twelve days later the crater was strikingly reduced in size."

Bottom: "Two weeks later another spot roentgenogram revealed complete healing."

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J. L., male, age 39, refused surgery even though roentgen study revealed a huge ulcer crater in the duodenal bulb (top left). He was placed on a Pro-Banthine regimen of 30 mg. four times a day. After twelve days of therapy the crater was strikingly reduced in size (top right).

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SCHEDULE OF POSTGRADUATE COURSES, AUTUMN, 1953

The following courses have been arranged through the generous cooperation of the directors and the institutions at which the courses will be given. Tuition fees for all courses will be: Members, $30.00; Non-members, $60.00. Full details of these courses may be obtained through the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa.

No. Course	October				November					December				January 1954		
	5–10	12–17	19–24	26–31	2–7	9–14	16–21	23–28	Nov. 30–5	7–12	14–18	21–26	28–Jan. 2	4–9	11–16	
1. **CARDIOVASCULAR DISEASES:** New York University College of Medicine, New York, N. Y.; Charles E. Kossmann, M.D., F.A.C.P., Director		X						Thanksgiving Week, November 26	A.M.A. Interim Session, St. Louis—Nov. 30–Dec. 5			Christmas Week	New Year's Week			
2. **PHYSIOLOGICAL BASIS OF INTERNAL MEDICINE:** Duke University School of Medicine, Durham, N. C.; Eugene A. Stead, Jr., M.D., F.A.C.P., Director		12–16														
3. **INTERNAL MEDICINE:** University of Chicago School of Medicine, Chicago, Ill.; Wright R. Adams, M.D., F.A.C.P., Director			19–23													
4. **CLINICAL NEUROLOGY:** Jefferson Medical College of Philadelphia, Philadelphia, Pa.; Bernard J. Alpers, M.D., F.A.C.P., Director					2–6											
5. **PRESENT DAY THERAPY AND ITS PHYSIOLOGIC BASIS:** University of Utah College of Medicine, Salt Lake City, Utah; Maxwell M. Wintrobe, M.D., F.A.C.P., and Louis S. Goodman, M.D., Co-Directors						9–13										
6. **SEMINARS IN INTERNAL MEDICINE:** Vanderbilt University School of Medicine, Nashville, Tenn.; Rudolph Kampmeier, M.D., F.A.C.P., and Hugh J. Morgan, M.D., F.A.C.P., Co-Directors							16–20									
7. **THE NEWER BIOLOGICAL AND PHYSIOLOGICAL APPROACHES TO CLINICAL PROBLEMS:** University of Wisconsin Medical School, Madison, Wis.; William S. Middleton, M.D., M.A.C.P., and Karver L. Puestow, M.D., F.A.C.P., Co-Directors						16–20										
8. **BALLISTOCARDIOGRAPHY:** Johns Hopkins Hospital, Baltimore, Md.; Benjamin M. Baker, Jr., M.D., F.A.C.P., Director															11–13	

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Usual dosage 1 or 2 tablets 4 times a day

Bibliography: 1. Humphreys, P., et al.: Angiology 3:1 (Feb.) 1952. 2. Plotz, M.: New York State J. Med. 52:2012 (Aug. 15) 1952. 3. Dailhou-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.

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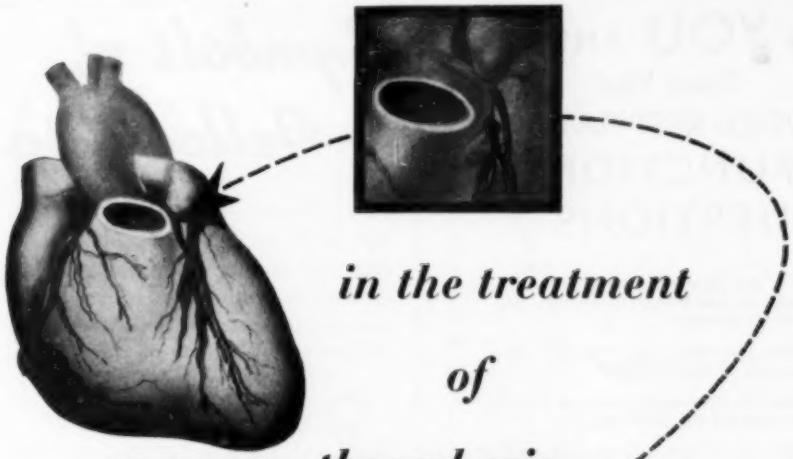
INDEX TO ADVERTISERS

September, 1953

Abbott Laboratories 55
American Bakers Association 30
Ames Company, Inc. 8
Appleton-Century-Crofts, Inc. Second cover
Armour Laboratories, The 59
Ayerst, McKenna & Harrison Limited . 23
Ernst Bischoff Company, Inc. 41
Brewer & Company, Inc. 18
Briggs Company, The 6
Burroughs Wellcome & Co. (U.S.A.) Inc. 38
Burton Parsons & Co. 32
Chicago Dietetic Supply House, Inc. .. 4
Ciba Pharmaceutical Products, Inc. .. 9, 37
Warren E. Collins, Inc. 58
Davies, Rose & Company, Limited 35
Dietene Company, The 45
Eaton Laboratories, Inc. 12–13
Geigy Pharmaceuticals 57
General Electric Company, X-Ray Dept. 22
Paul B. Hober, Inc. 3
Hoffman-La Roche, Inc. insert facing page 8
Irwin, Neisler & Co. 15, 54
Lea & Febiger 4
Thos. Leeming & Co., Inc. 43
Eli Lilly and Company 5
Lloyd Brothers, Inc. 60–61
Macmillan Company, The 1
S. E. Massengill Company, The .. 31, 40, 51
Mead Johnson & Company 46
Medical Protective Company, The 2
Merck & Co., Inc. 34
Wm. S. Merrell Co., The 28–29
Oxford University Press, Inc. 2
Parke, Davis & Company 33
Pfizer Laboratories, Division, Chas. Pfizer & Co., Inc. 10, 19–20–21, Third cover
Pitman-Moore Company 25
William H. Rorer, Inc. 52
Sanborn Co. 42
San Joaquin General Hospital 2
Schenley Laboratories, Inc. 16–17
Schering Corporation 27
G. D. Searle & Co. 49
Sharp & Dohme, Inc. 48
Smith, Kline & French Laboratories ... 14
E. R. Squibb & Sons, Division of Mathieson Chemical Corporation 26
U. M. A. Inc. 62
Upjohn Company, The 24
Varick Pharmacal Co., Inc. 44
Warner-Chilcott Laboratories, Inc. .. 7, 53
Winthrop-Stearns Inc. 47
Woodward Medical Personnel Bureau . 6
Wyeth Incorporated 11, 39



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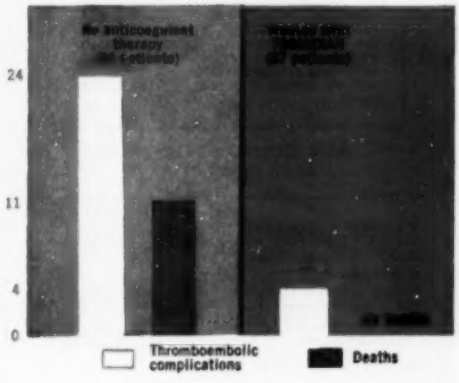

1. Tulloch, J. A., and Gilchrist, A. R.: Tromexan in the Treatment of Coronary Thrombosis, Am. Heart J. 42:864, 1951.

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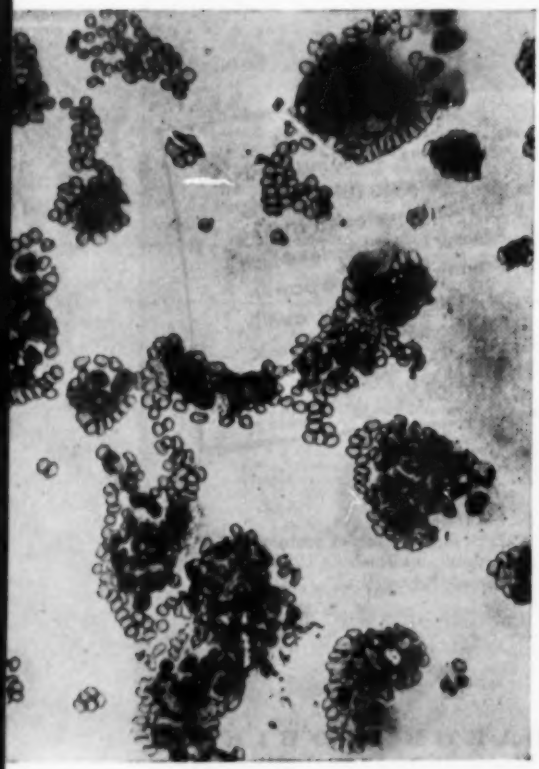
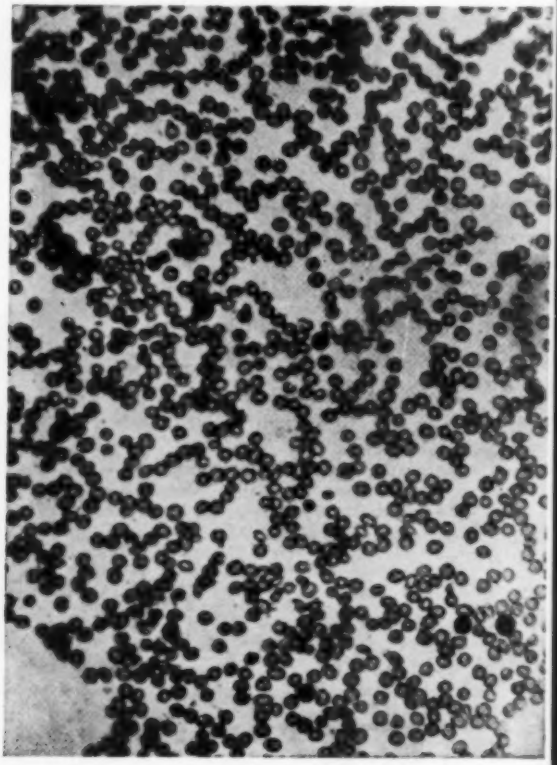


Bone marrow showing—acquired erythrocytic hypoplasia—no nucleated erythrocytes.



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1. Case 2, Seaman, A. J., and Koler, R.; Acta Hematologica, 9:153, 1953.

2. Gardner, Frank H., J. Lab. Clin. Med.; 41:56, 1953.

3. Rohn, R. J. and Bond, Wm. H.; J. Lancet, 73:301, 1953.

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